Cardiac Index as a Correlate of Brain Volume. Separating the Wheat of Normal Aging From the Chaff of Vascular Cognitive Disorders

Clinton B. Wright and Ralph L. Sacco

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The importance of vascular risk factors in the development and progression of cognitive disorders is gaining appreciation; the term “vascular cognitive disorders” refers to the common situation in which vascular damage plays a role, either alone or in combination with a neurodegenerative or other process, in the development of cognitive impairment or dementia. Numerous vascular risk factors have been implicated in vascular cognitive disorders, and many of these have been linked to cognitive decline through white matter damage and brain atrophy.1–8 As the American Heart Association launches its new strategic plan to improve the cardiovascular health of all Americans by 20%, a greater focus on ideal cardiovascular health will likely lead to improved brain health and therefore cognitive health. To address the health needs of our aging population, a better understanding of the links between cardiovascular disease and brain structure and function will be required. In addition, it will be important to identify early markers of unsuccessful aging to test interventions that can improve outcomes.

Various quantitative measures are now available to help us understand the relationships between vascular disease and brain health. These include neuropsychological testing, structural and functional magnetic resonance imaging, and metabolic imaging with magnetic resonance imaging and positron emission tomography. These tools have helped us better quantify changes in brain structure and metabolism and relate them to associations between aging, neurovascular risk factors, and cognitive function. In this issue of Circulation, Jefferson et al9 report an association between cardiac index and brain volume and relate these to cognitive function in a subsample of the well-characterized Framingham Study (participants were healthier than the overall cohort, being well enough to undergo magnetic resonance imaging). The brain volumes of participants were smaller among those with lower cardiac index values, even after adjustment for risk factors thought to be associated with brain volume loss, namely, age, sex, systolic blood pressure, smoking status, diabetes mellitus, hypertension treatment, atrial fibrillation, and prevalent cardiovascular disease. The authors concluded that subtle reductions in cardiac index are implicated in “accelerated brain aging.”9

A striking aspect of the study by Jefferson et al9 is the suggestion that even intermediate reductions in cardiac index were associated with reductions in brain volume. In their primary analyses, cardiac index was used as a continuous variable, although when they dichotomized at the clinical level used to define a low cardiac index, there was no relationship with brain volume. Post hoc analyses by tertiles of cardiac index showed a threshold effect: Participants with a cardiac index in the middle tertile had mean brain volumes corrected for head size that were just as low as those in the lowest tertile. In population-based studies, we tend to think that extremes are bad and the middle is good, but in this study, it was possible to associate the brain volumes of two thirds of a relatively healthy population with the cardiac index exposure. It is somewhat surprising that no dose response was seen, and it is not clear whether dividing cardiac index values into quartiles or quintiles or using another method such as spline curves would have disclosed an underlying dose effect in relation to brain volume. However, the effect modifications by age and sex show heterogeneity in the sample, and it appears that the findings applied mostly to participants less than 60 years of age, and to men rather than women. We agree with the authors that the association between cardiac index and brain volume may not have been discernible among older participants owing to other competing factors; however, given that the models were fully adjusted for potential confounders, including vascular risk factors that arguably exist on the causal pathway of interest, we wonder whether overadjustment minimized the effects in those for whom vascular risk factors were most tied to the association between cardiac index and brain volume.10 However, an association between cardiac index and brain volume in those less than 60 years of age strengthens these results.

Untangling the importance of brain volume in cognitive function is a challenge in living subjects, because participants must be followed up for years, or even decades depending on the baseline age, to determine whether they age normally or develop dementia. Alzheimer disease is the most common cause of dementia in older people who are followed up long enough, but it is often mixed with vascular damage. Early on, when cognitive changes are minimal, it is often not possible to distinguish differences in brain volume caused by aging.
neurodegenerative diseases, and vascular damage. In the end, diagnostic certainty relies on pathology, but few large-cohort study participants undergo autopsy, and we must largely depend on longitudinal studies to map the brain volume losses in areas preferentially affected by these processes.

In the case of the study by Jefferson et al, a combination of aging, vascular damage, and a propensity toward Alzheimer disease is most likely to be operative. The regional brain volume losses associated with each of these processes are not well understood, but increasing evidence suggests that microvascular damage leads to white matter damage and preferentially affects the frontal lobes (and frontal lobe function), whereas the temporal and parietal lobes are most susceptible to Alzheimer disease. Of particular note, the authors found no association between cardiac index and white matter lesion load, commonly believed to be a measure of small-vessel damage in the brain, and they also found no direct association with frontal lobe volumes. The authors did find an association between a low cardiac index and worse performance in specific cognitive domains. Although these differences by examining regional brain volumes aging. The authors did an excellent job of trying to understand these differences by examining regional brain volumes and performance in specific cognitive domains. Although they provide background data linking low cerebral perfusion to Alzheimer disease, they did not find evidence that cardiac index was associated with either hippocampal volumes or memory scores.

Patients with perfusion failure due to low systemic blood pressures, such as occurs in heart failure, can experience tissue injury and cognitive decline. Indeed, cognitive decline due to heart failure has generated great interest because it may be reversible, and it is of great importance to identify markers of cognitive dysfunction at the earliest stages if there is therapeutic potential. However, less is known about the relationship between subclinical reductions in cardiac function in normal populations.

Cerebral perfusion and metabolism are inextricably linked. In neurodegenerative processes such as Alzheimer disease, decreased neuronal function requires less energy. Cerebral perfusion is reduced because less blood is demanded by affected brain tissue. The opposite is true in cerebral ischemia: Decreased blood flow below a critical threshold causes tissue injury that results in a decrease of brain metabolism in surviving damaged areas. However, blood flow reductions short of ischemia are of uncertain consequence. To prevent damage to brain tissue caused by variations in blood pressure (either too high or too low), cerebral arteriolar size is moderated (a process called autoregulation) to maintain perfusion within safe limits. When mean blood pressure drops below ≈60 mm Hg, autoregulation fails, and cerebral perfusion begins to drop to levels that cause, sequentially, inhibition of protein synthesis (35 to 55 mL·100 g⁻¹·min⁻¹), a shift to anaerobic glycolysis (20 to 35 mL·100 g⁻¹·min⁻¹), and energy failure (10 to 12 mL·100 g⁻¹·min⁻¹), the end result of which is infarction. Chronic hypertension may shift the autoregulatory curve such that a higher blood pressure must be maintained, below which cerebral perfusion becomes inadequate. Thus, in the normal brain, autoregulation helps compensate for reduced systemic perfusion (ie, lower cardiac index) and allows it to resist acute injury from drops in blood pressure. The effects of aging on neuronal-vascular integrity and the duration of reduced systemic perfusion may alter these normal responses, but these relationships require clarification. The prevalence of clinical heart failure in this Framingham sample was low (6%) and thus did not account for the observed differences in brain volume. Jefferson et al argue that reduced systemic blood flow “directly reduces cerebral perfusion” and can thereby cause subclinical brain injury, which suggests that normal autoregulation fails at some level to protect the brain. Although hypovolemia has been shown to result in reductions in both cardiac output and cerebral blood flow in cats, the connection between reductions in cardiac output and cerebral perfusion in humans, especially within the range of autoregulation, is not well worked out (the authors quote a study in Macaques, but cardiac output in these animals was not reduced below baseline levels, and reductions in cerebral perfusion were seen only in the experimentally infarcted hemisphere). As the authors acknowledge, this cross-sectional study cannot make claims about causation, and the more than 3 years on average between brain and cardiac magnetic resonance studies complicates this a bit further. Prospective studies with longitudinal measures of brain and cardiac function are needed to confirm these results.

It will take years to know the fate of all 1504 Framingham participants in the study by Jefferson et al. Whether lower cardiac index leads to reduced brain volumes and accelerates neurodegeneration on an eventual path to dementia is not yet clear. What is known is that various vascular risk factors, including decrements in cardiac function, are determinants of dementia (both Alzheimer disease and variants of vascular cognitive disorders). This provides opportunities to find interventions that modify the course of these diseases predicted to be of major impact on our aging population.

Disclosures

None.
References


