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

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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.<sup>1–8</sup> 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.

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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 al<sup>9</sup> 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.”<sup>9</sup>

A striking aspect of the study by Jefferson et al<sup>9</sup> 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.<sup>10</sup> 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,

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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,<sup>9</sup> 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 on their measure of executive function/information processing, which was attenuated after the exclusion of those with prevalent cardiovascular disease, which suggests that vascular factors may have played a role in this association. However, overall, this study does not support a connection between diminished cardiac index values and cognitive dysfunction through small-vessel damage.

The brain volume changes associated with normal aging are less clear. In a longitudinal Alzheimer's Disease Neuroimaging Initiative study of people who remained cognitively normal over 2 years, serial magnetic resonance imaging data have shown brain volume losses in the temporal and parietal lobes that were typical of Alzheimer disease, as well as in areas that may have been associated with aging (eg, prefrontal cortex, cerebellum, and thalamus).<sup>11</sup> The study by Jefferson et al<sup>9</sup> was cross-sectional, and therefore, the exclusion of participants with dementia does not mean that brain volume differences among the subjects were not due to underlying processes that could later result in dementia. On the flip side, brain volume differences could also have been due to normal 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.<sup>12–15</sup> 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  $\approx 60$  mm Hg, autoregulation fails, and cerebral perfusion begins to drop to levels that cause, sequentially, inhibition of protein synthesis ( $35$  to  $55 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ ), a shift to anaerobic glycolysis ( $20$  to  $35 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ ), and energy failure ( $10$  to  $12 \text{ mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ ), the end result of which is infarction.<sup>16,17</sup> Chronic hypertension may shift the autoregulatory curve such that a higher blood pressure must be maintained, below which cerebral perfusion becomes inadequate.<sup>18</sup> 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<sup>9</sup> 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).<sup>19,20</sup> 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.<sup>9</sup> 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

1. Knopman DS, Mosley TH, Catellier DJ, Coker LH. Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: the ARIC MRI Study. *Alzheimers Dement*. 2009;5:207–214.
2. Ott A, Slioter AJ, Hofman A, van Harskamp F, Witteman JC, Van Broeckhoven C, van Duijn CM, Breteler MM. Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: the Rotterdam Study. *Lancet*. 1998;351:1840–1843.
3. Mukamal KJ, Kuller LH, Fitzpatrick AL, Longstreth WT Jr, Mittleman MA, Siscovick DS. Prospective study of alcohol consumption and risk of dementia in older adults. *JAMA*. 2003;289:1405–1413.
4. Khatri M, Nickolas T, Moon YP, Paik MC, Rundek T, Elkind MS, Sacco RL, Wright CB. CKD associates with cognitive decline. *J Am Soc Nephrol*. 2009;20:2427–2432.
5. Luchsinger JA, Patel B, Tang M-X, Schupf N, Mayeux R. Measures of adiposity and dementia risk in elderly persons. *Arch Neurol*. 2007;64:392–398.
6. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med*. 2003;348:1215–1222.
7. Wright CB, Festa JR, Paik MC, Schmiedigen A, Brown TR, Yoshita M, DeCarli C, Sacco R, Stern Y. White matter hyperintensities and subclinical infarction: associations with psychomotor speed and cognitive flexibility. *Stroke*. 2008;39:800–805.
8. Knopman DS, Mosley TH, Catellier DJ, Sharrett AR. Cardiovascular risk factors and cerebral atrophy in a middle-aged cohort. *Neurology*. 2005;65:876–881.
9. Jefferson AL, Himali JJ, Beiser AS, Au R, Massaro JM, Seshadri S, Gona P, Salton CJ, DeCarli C, O'Donnell CJ, Benjamin EJ, Wolf PA, Manning WJ. Cardiac index is associated with brain aging: the Framingham Heart Study. *Circulation*. 2010;122:690–697.
10. Schisterman EF, Cole SR, Platt RW. Overadjustment bias and unnecessary adjustment in epidemiologic studies. *Epidemiology*. 2009;20:488–495.
11. Fjell AM, Walhovd KB, Fennema-Notestine C, McEvoy LK, Hagler DJ, Holland D, Brewer JB, Dale AM. One-year brain atrophy evident in healthy aging. *J Neurosci*. 2009;29:15223–15231.
12. Woo MA, Macey PM, Fonarow GC, Hamilton MA, Harper RM. Regional brain gray matter loss in heart failure. *J Appl Physiol*. 2003;95:677–684.
13. Siachos T, Vanbassel A, Feldman DS, Uber W, Simpson KN, Pereira NL. Silent strokes in patients with heart failure. *J Card Fail*. 2005;11:485–489.
14. Vogels RL, Oosterman JM, van Harten B, Scheltens P, van der Flier WM, Schroeder-Tanka JM, Weinstein HC. Profile of cognitive impairment in chronic heart failure. *J Am Geriatr Soc*. 2007;55:1764–1770.
15. Vogels RL, van der Flier WM, van Harten B, Gouw AA, Scheltens P, Schroeder-Tanka JM, Weinstein HC. Brain magnetic resonance imaging abnormalities in patients with heart failure. *Eur J Heart Fail*. 2007;9:1003–1009.
16. MacKenzie E, Farrar J, Fitch W, Graham D, Gregory P, Harper A. Effects of hemorrhagic hypotension on the cerebral circulation, I: cerebral blood flow and pial arteriolar caliber. *Stroke*. 1979;10:711–718.
17. Marshall RS, Lazar RM, Pile-Spellman J, Young WL, Duong DH, Joshi S, Ostapovich N. Recovery of brain function during induced cerebral hypoperfusion. *Brain*. 2001;124:1208–1217.
18. Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev*. 1990;2:161–192.
19. Tranmer BI, Keller TS, Kindt GW, Archer D. Loss of cerebral regulation during cardiac output variations in focal cerebral ischemia. *J Neurosurg*. 1992;77:253–259.
20. Davis DH, Sundt TM. Relationship of cerebral blood flow to cardiac output, mean arterial pressure, blood volume, and alpha and beta blockade in cats. *J Neurosurg*. 1980;52:745–754.

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