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Parameters of left ventricular mass and dementia: moving the literature forward

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Left ventricular (LV) hypertrophy is a marker of heart and other end-organ damage. It reflects chronic exposure to multiple cardiovascular risk factors, including sustained arterial hypertension.[1] In 1987, prevalence estimates of LV hypertrophy ranged from 23 to 43 percent in persons with moderate to severe hypertension.[2] Not only is LV hypertrophy a risk factor for cardiovascular pathology and brain injury,[1] it is also a risk factor for lowered levels of cognition and all-cause probable dementia.[3] The possibility of an LV hypertrophy-dementia association was first raised in a study by Kahonen-Vare et al. (2004).[4] These investigators reported a two-fold increase in the concurrent diagnosis of dementia in persons exhibiting LV hypertrophy, although concurrent relations do not rule out a bidirectional relationship between these variables. A prospective design with longitudinal tracking of dementia is necessary. In the Rotterdam Study,[5] LV hypertrophy was associated with a 5-year decline in performance on a dementia rating scale, but evidence of data from a rating scale is incomplete. The paper by Moazzami et al. in this issue of *Hypertension* is the first to reveal a positive prospective association between LV mass and probable dementia defined by hospital records.[6]

The Moazzami et al. study employed a large (n=4999), ethnically diverse U.S. sample from the Multi-Ethnic Study of Atherosclerosis (2000 to 2012). Cardiac magnetic resonance imaging, a technique superior to imaging techniques used in previous research, was used to obtain multiple measures of LV structure and function at baseline. Participants were contacted every 9 to 12 months during the study period to identify incident cases of probable dementia and cognitive function was assessed at the last follow-up examination using the Cognitive Abilities Screening Instrument, Digit Symbol Coding, Digit Span Forward and Digit Span Backward.

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With adjustment for demographics and cardiovascular risk factors, diastolic function, LV structure and LV sphericity volume at end-diastole were significantly associated with probable dementia risk. Risk was increased in participants with higher strain relaxation index (hazard ratio [HR]=1.60) and decreased in participants with higher early diastolic strain rate (HR=0.58). Higher LV mass index, a measure of hypertrophy, and mass-to-volume ratio, a measure of concentric remodeling, were associated with increased risk of probable dementia (HR=1.01 and HR=2.31, respectively). For those who completed magnetic resonance imaging tagging, first and last quintile of sphericity volume index were also associated with increased risk of probable dementia (HR=8.19). It is important to note that this estimate had a large 95% confidence interval (2.1 to 59.6), which could reflect the low incidence rate of dementia (2.67% of the sample) or collinearity in the extensive regression model employed. Thus, while the associations are very likely significant, risk is not yet precisely estimated.

LV mass index and mass-to-volume ratio were negatively associated with performance on each cognitive measure (all $p<0.05$), just as they were associated with increased risk for probable dementia. This suggests that some of the individuals performing less well are on a trajectory for dementia. Findings for the cognitive measures are consistent with a comprehensive review of the literature by Wendell and Waldstein (2015).[3] It is important to emphasize that LV structural and functional parameters were examined in relation to cognitive performance, not cognitive impairment. Evidence for an association between LV mass and cognitive impairment comes from the dementia findings. In the following section, we comment on directions for future studies designed to fill in gaps in knowledge with regard to dementia and measures of brain injury corresponding with cognitive deficits.

Gaps in knowledge and future studies

Assessing dementia in a community-based sample

Identifying cases of probable dementia using hospital records is an improvement over dementia rating scales, it is not optimal. In the Moazzami et al. study, probable dementia was identified using International Classification of Diseases-9 hospital codes. As Moazzami et al. have emphasized in their paper and others have noted[7], this method of ascertaining dementia status may underestimate incidence because this technique only identifies subjects who are hospitalized and for whom dementia is included among their discharge diagnoses. The argument that using hospital samples underestimate dementia is consistent with the low prevalence of dementia in the Moazzami et al sample, i.e., 2.67% of total sample; mean age for participants with dementia: 73±7 years. An extensive and comprehensive review by Prince et al. (2013) indicates an all-cause prevalence of 6.4 percent in US citizens over 60 years of age.[8] We strongly encourage future studies involving community based samples and employing the comprehensive methods of dementia recognition and diagnosis employed in the Framingham Study or other major studies of dementia.[9]

Differentiating between types of dementia

A more broadly-based limitation of all studies to date is the focus on all-cause dementia rather than separately assessing Alzheimer's disease, vascular dementia, and mixed

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dementia. These studies are important for determining the specific role played by cardiovascular disease, including LV hypertrophy, in the progression from normal cognitive functioning to dementia. The question is important because cardiovascular disease is preventable and reversible, whereas currently brain pathology more prevalent in purer forms of Alzheimer's disease is not. Some investigators have argued that hypertension and cardiovascular disease are more dominate in the prodromal stages of vascular dementia than Alzheimer's disease. This is an important yet unconfirmed hypothesis. The Moazzami et al. study gives us a sensitive set of tools (LVM parameters) to help answer the question and to advance our understanding of the role of heart disease in dementia.

Corollary measures of brain injury

While cardiac magnetic resonance imaging was used to identify important LV mass parameters, brain neuroimaging was not used to confirm presence of dementia, nor to relate the regional functional and structural variables and dementia to brain injury. But the work by Moazzami et al. sets the stage for these studies. For example, Nakanishi et al. (2017) examined 665 participants in the Cardiovascular Abnormities and Brain Lesions study who had undergone transthoracic echocardiology and brain imaging.[10] Patients were separated into normal geometry, concentric remodeling, concentric hypertrophy, and exocentric hypertrophy. Ninety-four participants exhibited silent brain infarction. The highest risk for both silent brain infarction (OR= 3.39) and upper quartile of log white matter hyperintensities volume (OR = 3.35) was associated with concentric hypertrophy, and the second highest risk for silent brain infarction and white matter hyperintensities was associated with eccentric hypertrophy (OR= 2.52 and 1.96). It is well known that brain infarction and white matter volume play an important role in cognitive impairment and dementia and may mediate associations between hypertension and cognition.[1, 11]

Summary and Treatment Implications

The Moazzami et al. study has reactivated an interest in LVM and cognitive performance and has extended this literature to include an examination of LVM and probable dementia. More importantly, it is the first study to reveal a positive prospective association between important specific parameters of LV mass and probable dementia. These associations were examined in a large, ethnically diverse sample and parameters of LV structure and function were assessed using state-of-the-art imaging techniques. Findings from the study call attention to the importance of early detection, prevention and reversal of LV hypertrophy in order to prevent or slow the progression of dementia. This goal is within reach. In the Systolic Blood Pressure Intervention Trial (n=7569), BP lowering was associated with 46 percent reduction of risk for developing LV hypertrophy.[12] LV hypertrophy patients assigned to intensive treatment were also 66% more likely to show regression of LV hypertrophy compared to controls. It is our hope that the Moazzami et al. study will stimulate further research in this area using the more precise measures of LVM introduced in the study.

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