The arterial system gradually stiffens because of the time integrated and shared effects of several traditional risk indicators. In clinical practice, this detrimental process can be monitored noninvasively by the carotid-femoral pulse wave velocity (cf-PWV), which is considered the “gold standard” methodology for the stiffness of the thoracic and abdominal aorta. PWV improved cardiovascular risk prediction when added to standard risk factors including systolic blood pressure in several community-based samples including the Framingham Heart Study.

Stiffening of the arterial wall is increasingly considered as a hallmark of unsuccessful aging and shifted our interest to interactions between the fields of arterial stiffening and hypertension and the fields of subtle brain damage and mild cognitive impairment/dementia on the other side. A decade of intensive research linked increased cf-PWV with a higher prevalence and extent of brain lesions on nuclear magnetic resonance imaging (MRI) and lower cognitive scores on a whole array of neuropsychological tests, however, with varying degrees of uncertainty.

In the meta-analysis by van Sloten et al., arterial stiffness studies with cognition-related outcomes showed considerable heterogeneity. Some of the studies showed significant associations with cognitive impairment but many associations were relatively weak. The weakest evidence is expected for less specific and less precise measurements of cognitive function (eg, scrutinizing Mini-Mental Status Examination). Relative strength of the associations might have been weakened by competing conditions, such as atherothrombosis and neurodegenerative diseases.

Hajjar et al. demonstrated that PWV is superior to elevated blood pressure in predicting hypertension-related cognitive decline. Higher PWV was associated with a steeper decline in executive, memory, and working memory scores after appropriate adjustments. PWV increased the explained variance of the association between hypertension and executive function from 1% to 10%.

In the same meta-analysis by van Sloten et al. on 23 studies, greater stiffness was associated more convincingly with markers of cerebral small vessel disease (CSVD) with odds ratios all around 1.30 per 1 SD increase in the cross-sectional analyses: 1.30 for white matter hyperintensities (WMH), 1.32 for cerebral microbleeds, and 1.29 for cerebral infarcts. Of interest, the Framingham Heart Study confirmed significant associations between cf-PWV and lower total cerebral brain volume, greater WMH volume, and greater prevalence of silent cerebral infarcts. Nonetheless, a word of caution might be in place as in a more recent study of elderly without cognitive impairment the significance for a crude analysis between cf-PWV and WMH was lost after adjustment for common cardiovascular covariates.

The large majority of these studies targeted elderly individuals because arterial stiffness, cognitive decline, and brain damage are traditionally viewed as inherent to irreversible processes of aging. Foci of ongoing research are: (1) is aortic stiffness an innocent bystander marker or a causal or mediating factor for deteriorating cognitive function and for an increasing burden of anatomic brain lesions? and (2) does the conversion to pathology start already at an early age?

One of the background assumptions is the higher vulnerability of small brain vessels to conditions of high pulsatile flow and pressure potentially leading to structural brain target organ damage including (without intending to be exhaustive) WMH, enlarged lateral ventricular volumes and perivascular spaces, cerebral microbleeds, brain atrophy, and (lacunar) infarcts each requiring specific MRI visualization techniques. White matter and basal ganglia are mainly perfused by penetrating branches from cerebral arteries and the circle of Willis, whereas the cerebral cortex is perfused from a pial network of circuitous muscular arteries. Therefore, there is a higher propensity for deep structure lesions (lacunes, WMHs, and perivascular spaces) if arterial stiffness were involved. In an editorial commentary, Mitchell nicely reviewed the role of aortic stiffness and pulsatile hemodynamics in CSVD as well as the reasons for the higher propensity. The cornerstone is that the microvessels of the brain (essentially a high flow region) are more prone to the direct consequences of large artery (aorta) stiffening. When the aorta stiffens (aging process), there is a reduced impedance mismatch between the low impedance aorta and the high impedance first-generation branch vessels. The consequence is reduced wave reflection at the boundaries leading to more straightforward transmission of energy to the microvessels that respond by vasoconstriction or remodeling. Thus, theoretically arterial stiffness might be a causal factor for CSVD but does that process start early?
In this issue of Hypertension, the Framingham Third-Generation Cohort Study investigators explored the cross-sectional associations between cf-PWV and cognitive function and brain aging in young adulthood and middle-aged individuals (mean age, 46 years). In adjusted regression models, higher cf-PWV was associated with poorer processing speed and executive function mainly in midlife, larger lateral ventricular volumes in young adulthood and a greater burden of WMH in middle-aged adults. In sharp contrast, brachial pulse pressure was not associated with any of the MRI outcomes. The authors called for prospective studies to examine whether aortic stiffening in young adulthood is associated with vascular cognitive impairment later in life.

The strong backbone of the Framingham Third-Generation Cohort Study, the in-depth clinical phenotyping, the large armamentarium of neuropsychological tests covering 4 broad abilities as defined in the Cattell–Horn–Carroll model (trail making for processing speed, visual processing, short-term memory and long-term storage and retrieval) and the MRI facility with 3-dimensional spoiled gradient echo acquisition and fluid-attenuated inversion recovery sequences are among the strengths of the study to be illuminated. The authors broaden the field by calling into question the paradigm that increased PWV and unsuccessful brain aging are only an issue after midterm. It is a clear hypothesis worthwhile to consider in future prospective studies, but their study is not free of limitations and may have interpretations and extrapolations that go too far. For instance, the postulated explanations for the absence of a significant association between cf-PWV and WMH in early adulthood and lateral ventricular volumes in middle-aged individuals are theoretically likely albeit still speculative. Indeed, MRI techniques may lack sensitivity to detect subtle brain damage preceding important WMH in young adults and in midlife time-integrated effects of traditional risk factors may become stronger at the expense of the significance level for the volumes. Confirmation of the hypothesis is needed in other population-based samples as the study could not rule out age-specific associations because of chance. Moreover, there was only one sound association in young adulthood (with lateral ventricular volumes). Final evidence is lacking that cf-PWV would be an independent predictor of MRI and cognitive outcomes (cost-effective strategies?) in young and middle-aged individuals. What is the likelihood that cf-PWV will offer more than an early biomarker of CSVD? After confirmation that minimal brain lesions and cognitive decline in vulnerable individuals start from early adulthood the question remains whether arterial stiffness is already mechanistically involved (causality or mediation) in that age category.

Recently, Marfella and Paolisso discussed several potential mechanisms by which arterial stiffness would contribute to cognitive impairment and incriminated subtle effects of shear stress and oxidative stress/inflammation in low-risk populations. Earlier, there have been reports on repeated episodes of microvascular cerebral ischemia/hypoperfusion and impaired cerebral vasoreactivity amplified by blood pressure variability. In older adults from the Age, Gene/Environment Susceptibility (AGES)–Reykjavik Study, cerebral microvascular remodeling and parenchymal damage (cerebrovascular resistance and WMH) were the inferred mechanisms that mediated the associations between cf-PWV and memory. There is a reasonable evidence that high blood pressure is mechanistically involved in CSVD. In the Northern Manhattan Study (NOMAS) cohort, WMH and lacunar lesions presumably ischemic were somewhat better interrogated by mean blood pressure, whereas enlarged perivascular spaces were somewhat better interrogated by pulse pressure.

“Gold standard” cf-PWV is the best documented stiffness-related parameter in clinical settings but by no means the only available one. First one should bear in mind that the Framingham Studies consistently and successfully used a specific formula for cf-PWV without a direct measure of the path length and the use of its 0.8 correction factor for compiling disparate data sets. Although not without fundamental criticism, other modifications of PWV (eg, ba-PWV) have been advocated. In the Second Manifestation of Arterial Disease–Magnetic Resonance (SMART-MR) Study, more complex stiffness parameters of the common carotid arteries (distensibility, compliance, Young and Peterson modulus, and stiffness index) were tested in relation with progression of total brain, cortical gray matter, ventricular and total white matter lesion volumes, and both lacunar and nonlacunar infarcts, but the yield of sound associations was meager.

What are the perspectives? Therapeutic interventions directly and simultaneously targeting arterial stiffness, CSVD, and cognitive impairment/dementia are still far away. Thus, the search for modifiable novel risk indicators has become a holy grail at the time being. However, in the foreseeable future, traditional risk factor-related preventive strategies might still be the most promising route to delay and retard these processes. The study by Pase et al in the Framingham Third-Generation Cohort Study should remind us that the association between aortic stiffness and unsuccessful brain aging is not confined to elderly only. They provided some proof-of-concept evidence and launched a call to broaden the horizon and focus both experimental and clinical research on the question whether aortic stiffness present in early adulthood will cause CSVD and cognitive impairment in later life.

Disclosures

None.

References


Young Adults With Stiff Arteries: Do They Have to Worry About Their Cognitive Function?
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