

Arterial stiffness and cognitive dysfunction in alzheimer and parkinson's diseases

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ABSTRACT

Cognitive dysfunction and dementia are important causes of disability and mortality in the elderly population. Over a decade, many studies have found evidence that greater arterial stiffness is associated with impaired cognitive function. Stiff arteries have a direct effect on the brain microvasculature. In this review, we present evidence that arterial stiffness is linked to cognitive dysfunction in neurodegenerative disorders represented by Alzheimer's disease and Parkinson's disease. We also discuss possible mechanisms of arterial stiffness and cognitive dysfunction other than the universal pathologic features of beta-amyloid for Alzheimer's disease and alpha-synuclein for Parkinson's disease.

Introduction

Cognitive impairment and dementia are common in the elderly and show increasing prevalence in the current society with the growing proportion of people of advanced age. Cognitive impairment is associated with increased deficits in activities of daily living¹ and is also an important predictor of morbidity and mortality². Vascular risk factors including hypertension, diabetes mellitus, and dyslipidemia have a potent role in cognitive impairment and dementia²⁻⁴.

Arterial stiffness is a marker of vascular aging and dysfunction⁵ and a strong predictor of cardiovascular diseases and mortality⁶. Many investigations have suggested that arterial stiffness is a predictor and risk factor of cognitive impairment and dementia⁷⁻²⁶. The aim of this study is to review the relationship between arterial stiffness and cognitive impairment in neurodegenerative diseases including Alzheimer's disease (AD) and Parkinson's disease (PD).

Arterial stiffness

The arterial system starts in the heart and terminates at the peripheral microvascular flow²⁷. The proximal large artery has elasticity and absorbs blood flow pressure from the heart, reducing blood flow pressure in the peripheral artery and end organ²⁷. The distensibility of the artery is inversely related to the arterial pulse wave: increased pulse wave velocity (PWV) is associated with a stiffer artery²⁸. As the artery becomes older, its cushioning function is decreased and the stiffer artery leads to reduced absorption of blood flow pulsatility, resulting in pulsatile flow to organs with a high oxygen demand such as the brain and kidneys²⁷. Arterial stiffness causes the pulse wave to flow faster and increases left ventricular load, leading to left ventricular dysfunction and cardiac failure²⁷. Reduced diastolic aortic pressure decreases the coronary artery perfusion pressure and causes myocardial ischemia²⁷.

Increased pulsation due to a stiffened artery enters into the microvascular system and predisposes arterial walls to rupture, resulting in the development of microinfarcts and microhemorrhages in brain and kidneys²⁷.

Measurement of PWV is generally accepted as the most simple, non-invasive, robust, and reproducible method to determine arterial stiffness²⁹. The brachial artery to ankle (baPWV) and carotid artery to femoral artery (cfPWV) are most widely used methods²⁸. Central pulse wave analysis and augmentation index are other indirect methods to measure arterial stiffness²⁹. However, PWV is a precise and simple test and has been used most widely in studies of arterial stiffness and cognitive impairment.

Atrial stiffness and cognitive dysfunction in Alzheimer's disease

Many cross-sectional studies have reported the association between arterial stiffness and cognitive function. Atrial stiffness was associated with subjective memory impairment, mild cognitive impairment (MCI), and dementia²⁶. A previous study of 84 subjects found that cfPWV was inversely correlated with results of the Mini Mental Status Examination (MMSE)⁷. In 352 elderly community-dwelling individuals, the middle tertile of baPWV was an independent risk factor for a low MMSE score (odds ratio = 9.66, 95% confidence interval (CI) = 1.15-80.93)⁸. Other authors studied 308 elderly subjects with memory impairment, who were categorized into MCI, AD, vascular dementia, and normal cognition⁹. PWV was significantly higher in subjects with vascular dementia or AD than in those with normal cognition ($p < 0.0001$) and PWV was higher in subjects with MCI than in those with normal cognition ($p = 0.01$) [9]. A community-based study with 203 subjects found that baPWV was significantly increased in the low MMSE score group ($p = 0.003$)¹⁰. A large population-based study with 3,714 subjects demonstrated that increased cfPWV was associated with worse performance on the Stroop test ($\beta = -1.13$; 95% CI = 0.26; 1.99)¹²; however, PWV was not associated with MMSE, letter digit substitution task, and word fluency test¹². In a study of 110 non-diabetic, never-treated patients with essential hypertension, increased cfPWV was associated with low MMSE score (0.36; $p = 0.026$)¹³. A re-designed cross-sectional study with 409 patients was conducted with detailed cognitive tests including visuospatial organization (block design, object assembly, visual reproductions immediate and delayed, Hooper visual organization test, and matrix reasoning), scanning and tracking (trail making tests, digit symbol substitution, and symbol search), verbal episodic memory (immediate and delayed Hopkins verbal learning test), working memory (digit span forward and backward, letter-number sequence, and controlled oral word associations), and global composite score¹⁵. Carotid-femoral PWV was associated with worse performance on visuospatial

organization, verbal memory, and global cognitive function ($p < 0.05$)¹⁵. An increase in PWV with age was also associated with a decrease in cognitive performance¹⁵. One substudy with 552 participants showed similar results¹⁶. After adjusting for other confounding factors, increased PWV had association with worse score in MMSE ($\beta = -0.55$; 95% CI = -0.91; -0.19), psychomotor speed (boxes and digit copying test, $\beta = -1.59$; 95% CI = -3.03; -0.15), and perceptual speed (pattern and letter comparison test, $\beta = -0.60$; 95% CI = -0.98; -0.22), but no association with verbal memory (Buschke selective reminding test, $\beta = -0.20$; 95% CI = -0.44; 0.04)¹⁶. One community-based study showed no association between PWV and cognitive function; of 319 participants aged 70-90 years, cfPWV had no significant association with indicators of cognitive function including processing speed (digit symbol coding and trail making test A), memory (logical memory Story A, Rey auditory verbal learning test, and the Benton visual retention test), language (animal naming and the 30-item Boston naming test), executive function (phonemic fluency, trail making test B, and the Stroop test), visuospatial function (block design), and global composite score¹⁹. In another large cohort of older adults, 1,436 participants were assessed for MMSE score, executive function, attention, speed, memory, and semantic memory²⁰. High cfPWV was associated with worse performance on the MMSE ($\beta = -0.31$; $p = 0.005$), Rey auditory verbal learning test ($\beta = -1.10$; $p = 0.01$), and the composite cognition score ($\beta = -0.10$; $p = 0.04$), whereas carotid-radial PWV had no association with cognitive dysfunction²⁰. A recent community-based cohort study with 1,101 subjects showed the risk associated with arterial stiffness²². Higher continuous cfPWV increased the risk of MCI ($p < 0.03$), but not all-cause dementia and Alzheimer's disease²². Arterial stiffness was an independent predictor of MCI²². Another recent study revealed that higher arterial stiffness was associated with MCI²³. In 4,461 subjects, the highest quartile of cfPWV was associated with a greater prevalence of MCI than the lowest quartile of cfPWV in white individuals (odds ratio = 1.27; 95% CI = 1.02; 1.56)²³. Arterial stiffness was associated with cognitive dysfunction in patients with subjective memory complaints. In 198 elderly patients with hypertension, cfPWV was the only significant predictor for memory impairment of men (odds ratio = 1.22; 95% CI = 1.00; 1.49, $p = 0.05$)²⁴. Higher cfPWV, normalized for mean blood pressure, was significantly associated with a lower MMSE score ($p < 0.05$) in 280 subjects with subjective memory complaints²⁵. Our recent study also showed that baPWV in subjects with subjective memory impairment was higher than healthy controls, although not statistically insignificant ($p = 0.058$)²⁶.

Several longitudinal studies have investigated the association between arterial stiffness and cognitive function. Most of these studies revealed that arterial stiffness was a potent predictor or risk factor for MCI

or dementia. In one study, during a mean follow-up of 4.4 years no associations were found between PWV and cognitive decline or risk of dementia¹¹. In another longitudinal study of 102 elderly subjects with 12 months of follow-up, cfPWV was related to a greater annual decline in MMSE score ($\beta = -0.736$; $p < 0.001$)¹². The authors concluded that PWV was a strong predictor of cognitive dysfunction¹². In addition, a longitudinal study performed over 14 years with 582 subjects revealed that PWV and cognitive decline were related¹³. Subjects with higher baseline cfPWV exhibited a prospective decline in verbal learning (California verbal learning test), delayed recall (California verbal learning test), nonverbal memory test (Benton visual retention test), and general cognitive screening test ($p < 0.05$)¹³. Moreover, another study analyzed the 1-year cognitive decline in nursing home patients with dementia who were older than 80 years¹⁷. Among 873 patients, increased cfPWV was associated with a greater decrease in MMSE ($p < 0.03$)¹⁷. A community-based study with 1,559 subjects demonstrated that higher cfPWV was not associated with memory (logical memory-delayed recall), and executive functions (trail making test part B minus part A score); however, increased cfPWV was associated with lower total cerebral brain volume, which is found in Alzheimer's disease ($p < 0.05$)¹⁸. A recent 5-year follow-up study was performed in community dwelling older adults²¹. The odds ratios for cognitive decline were higher in the highest tertile (2.95; 95% CI = 1.29; 6.74) and middle tertile (2.39; 95% CI = 1.11; 5.15) of baPWV, compared with the lowest tertile²¹. Therefore, high baPWV was an independent predictor of cognitive dysfunction²¹.

However, the pathophysiologic mechanisms linking arterial stiffness and cognitive dysfunction have not been determined. As stiffened artery causes loss of cushioning capacity, the increased pulsatile pressure and flow leads to increased vascular resistance and small vessel damage^{30,31}. The accumulated brain damage results in brain atrophy and cognitive dysfunction^{30,31}. Other suggested etiologies include heart diastolic dysfunction³², medial temporal lobe atrophy³³, reduced white matter integrity³⁴, increased white matter hyperintensities³⁵, progression of beta-amyloid deposition³⁶, and impaired renal function²⁶.

Arterial stiffness and cognitive dysfunction in Parkinson's disease

There are several reports on arterial stiffness in PD. In one study, measurement of cardio-ankle vascular stiffness index using PWV³⁷ in 63 PD subjects showed no difference in cardio-ankle vascular stiffness index compared with normal controls³⁷. Another study found that arterial stiffness was associated with cardiovascular autonomic dysfunction in patients with PD³⁶. Greater arterial stiffness was associated with orthostatic hypotension, supine hypertension, nocturnal hypertension, and nondipping³⁸.

A study including 27 patients with PD and five patients with multiple system atrophy showed that mean PWV at night was significantly elevated in patients compared with controls ($p = 0.04$)³⁹. In addition, cognitive dysfunction was related to neurocirculatory abnormalities⁴⁰. Cognitive impairment was associated with a reduction in blood pressure during orthostasis and an increase in systolic pressure while supine, and these blood pressure abnormalities were associated with elevated white matter hyperintensities⁴⁰. Arterial stiffness leads to cardiovascular autonomic abnormalities and causes white matter hyperintensities in brain, and therefore may be associated with cognitive dysfunction in PD.

We recently studied an association between arterial stiffness and cognitive dysfunction in patients with Lewy body disorder (LBD). In LBD patients, higher baPWV was associated with lower MMSE score ($\beta \pm SE = -0.003 \pm 0.001$, $p = 0.007$) and more severe dementia. Higher baPWV was also associated with lower performance in attention (digit span test), language (Korean Boston naming test), visuospatial function (Rey complex figure test), memory (Seoul verbal learning test), and executive function (control oral word association test) in LBD patients. This suggests that vascular brain injury is associated with cognitive dysfunction in LBD⁴¹.

Conclusion

This brief review highlights consistent findings that greater arterial stiffness is associated with cognitive dysfunction in normal elderly people, patients with subjective memory impairment, patients with MCI, and patients with AD. This supports the hypothesis that greater arterial stiffness has a potent role in microvascular brain damage and subsequent brain atrophy. However, strong evidence linking arterial stiffness and AD is lacking. Further longitudinal study is needed to investigate the effect of arterial stiffness on the development of AD. In addition, the role of arterial stiffness on cognitive dysfunction in PD should be further investigated.

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