Mini-Review

Aortic Stiffness, Cerebrovascular Dysfunction, and Memory

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Key Words

Aortic stiffness · Cognitive function · Memory · Pulsatile hemodynamics

Abstract

Background: Aortic stiffness is associated with cardiovascular and cerebrovascular events and cognitive decline. This mini-review focuses on relations of aortic stiffness with microvascular dysfunction and discusses the contribution of abnormal pulsatile hemodynamics to cerebrovascular damage and cognitive decline. We also provide a rationale for considering aortic stiffness as a putative and important contributor to memory impairment in older individuals. **Summary:** Aging is associated with stiffening of the aorta but not the muscular arteries, which reduces wave reflection and increases the transmission of pulsatility into the periphery. Aortic stiffening thereby impairs a protective mechanism that shields the peripheral microcirculation from excessive pulsatility within downstream target organs. Beyond midlife, aortic stiffness increases rapidly and exposes the cerebral microcirculation to abnormal pulsatile mechanical forces that are associated with microvascular damage and remodeling in the brain. Aortic stiffening and high-flow pulsatility are associated with alterations in the microvasculature of the brain; however, a mechanistic link between aortic stiffness and memory has not been established. We showed that in a community-based sample of older individuals, cerebrovascular resistance and white matter hyperintensities – markers of cerebrovascular remodeling and damage – mediated the relation between higher aortic stiffness and lower performance on memory function tests. These data suggest that microvascular and white matter damage associated with excessive aortic stiffness contribute to impaired memory function with advancing age. **Key Messages:** Increasing evidence suggests that vascular etiologies – including aortic stiffness and microvascular damage – contribute to memory impairment and the pathogenesis of dementia, including Alzheimer's disease. Interventions that reduce aortic stiffness may delay memory decline among older individuals.

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Introduction

Age is the foremost common risk factor for dementia. As the population ages, cognitive impairment is becoming more prevalent, resulting in a growing social and economic burden [1]. Along with degenerative changes in the brain, aging is associated with alterations in the structure and function of blood vessels, including a dramatic increase in aortic stiffness. Increased aortic stiffness is associated with elevated risk of incident cardiovascular and cerebrovascular disease events, including stroke [2–6]. Cerebrovascular pathologies are independently associated with cognitive dysfunction among the elderly. Oftentimes, vascular dysfunction manifests together with other disease markers, such as accumulation of β -amyloid plaques and tau protein tangles common to Alzheimer's disease (AD) [7, 8]. However, our current understanding of underlying mechanisms that link vascular dysfunction to age-related cognitive decline remains incomplete.

We recently examined the interrelations of aortic stiffness, microvascular dysfunction, and memory in a community-based sample of older individuals [9]. We found that markers of cerebrovascular remodeling and damage provide a putative mechanism whereby aortic stiffness may affect performance in memory function tests. Thus, small vessel disease (SVD) and white matter damage associated with excessive aortic stiffness contribute to impaired memory with age. Vascular risk factors that are prominently associated with various dementias, including AD, represent important independent and potentially modifiable targets for prevention and treatment [1, 10, 11]. The treatment options for aortic stiffness and their implications have been reviewed previously [12, 13]. The purpose of this review is to focus on the relation of aortic stiffness with microvascular dysfunction, to discuss the integral role of pulsatile hemodynamics and cerebrovascular damage in the pathogenesis of mild cognitive impairment and dementia, and to provide a rationale for considering aortic stiffness as a putative and important contributor to memory impairment in older individuals.

Aortic Stiffness, Impedance Matching, and Microvascular Dysfunction

Many methods of assessing arterial stiffness exist. Pulse wave velocity (PWV) is directly related to arterial stiffness and is easily assessed as the speed of a pulse wave traveling between two selected sites. The reference standard measure for aortic stiffness is carotid-femoral PWV (CFPWV), which is the measurement of PWV between the carotid and femoral arteries. CFPWV directly represents the stiffness of the thoracic and abdominal aorta and can be assessed noninvasively in the clinic using arterial tonometry and relatively modest equipment and expertise. Tonometric CFPWV is a potent novel indicator of cardiovascular disease (CVD) risk [4, 14]. Conversely, measures of muscular artery PWV, such as carotid-radial (muscular artery) and femoral-posterior tibial artery (femorotibial) PWV, which are much higher than CFPWV (aortic PWV) in young, healthy adults, are not related to incident CVD [4, 15].

Fragmentation of elastic fibers contributes to the progressive stiffening of the proximal aorta with age. The loss of elastic fibers is irreversible, which suggests that clinical and public health strategies should focus on primary prevention earlier in life. Over a lifetime, the proximal thoracic aorta bears the brunt of the pulsatile strain from cardiac ejection; therefore, the proximal aorta is susceptible to earlier deterioration than peripheral arteries. Elastic fiber fragmentation is associated with deposition and progressive engagement of much stiffer collagen fibers within the wall, ultimately stiffening the wall of the aorta and resulting in higher central pulse pressure, characteristic impedance, and PWV and altered timing of the reflected wave. In a study of the Framingham Offspring and Third Generation cohorts, aortic

stiffness, as assessed by CFPWV, was shown to increase modestly with age through midlife and dramatically thereafter [16]. An age-related increase in aortic stiffness is accompanied by only minor changes in the stiffness of muscular arteries [16, 17]. Stiffening of the proximal aorta, relative to the muscular and resistance arteries, increases the transmission of pulsatility into the microcirculation, resulting in target organ damage [17, 18]. Younger, healthy individuals, however, generally have a highly compliant aorta and relatively stiff muscular arteries, which creates a discontinuity of impedance to pulsatile flow at the transition between the aorta and first-generation arteries. This impedance mismatch reflects a portion of the pulsatile energy stored in the forward traveling wave, limiting its transmission into the peripheral vasculature. After midlife, the impedance of the aorta increases disproportionately to the muscular arteries, leading to impedance matching and a reduction in wave reflection. Thus, reduced proximal wave reflection associated with aging removes a protective mechanism that normally shields the peripheral microcirculation from excessive pulsatility.

In response to excessive pressure and flow pulsatility, the microvessels remodel and constrict. This compensatory mechanism protects the susceptible microcirculation from excessive pulsatile energy but also increases resistance and reduces blood flow [19, 20]. In the Framingham study, elevated aortic stiffness and increased pressure pulsatility were related to higher forearm vascular resistance at rest and blunted microvascular reactivity in response to ischemic stress [21]. Additionally, individuals with stiff arteries have a labile blood pressure, which may exacerbate the effects of blunted microvascular reactivity [22]. Thus, the initial cumulative sequelae of elevated aortic stiffness manifest as subclinical microvascular damage, which is a consequence of blood pressure lability, blunted microvascular reactivity, impaired autoregulation of organ blood flow, microvascular ischemia, and tissue damage [23].

Aortic Stiffness, Cerebrovascular Damage, and Memory

Recently, aortic stiffness has been associated with an increased risk for damage to microvascular structure and function of various target organs, including the kidneys and brain [9, 24–28]. Several factors, including blood-brain barrier and endothelial dysfunction, hypertension, hypercholesterolemia, diabetes mellitus, and smoking, contribute to cerebral SVD in older adults; however, the mechanisms by which aortic stiffness leads to cognitive dysfunction are complex and still incompletely understood. The brain is characterized by high flow, which requires low microvascular impedance. Since precapillary resistance provides the other major protection from pulsatile microvascular damage, the low-impedance brain circulation is particularly vulnerable to elevated pressure and flow pulsatility [18]. Elevated aortic stiffness and impedance matching drive the transmission of excessive pulsatile pressure and flow energy into the brain and damage small vessels and tissue.

The vascular hypothesis of AD is supported by studies of risk factors, but few have examined specific vascular properties that may mediate associations between vascular risk factors, memory impairment, and AD risk. Our research team recently investigated relations between aortic stiffness, microvascular damage, and cognitive function in the community-based Age, Gene/Environment Susceptibility – Reykjavik Study [9]. Multivariable models adjusted for vascular and cognitive risk factors showed that a higher CFPWV was related to lower memory scores but was not related to processing speed or executive function. Previous research suggests that vascular injury and ischemia of the brain manifest preferentially as a decline of executive function and processing speed rather than memory [28–32]. In our study, however, we found the strongest relations between aortic stiffness (CFPWV) and memory. Perhaps, in our cohort with a very high prevalence of hypertension and aortic stiffness, along

with their advanced age, the variability in vascular and cognitive measures is already reduced to a level that begins to obscure relations between stiffness and executive function or processing speed. Additionally, the loss of fiber tracts due to ischemic cerebrovascular injury in deep white matter may affect the integrity of gray matter regions associated with memory [33–36]. Particularly, function of the hippocampus has been shown more recently to be negatively associated with higher intracranial arterial flow pulsatility in elderly individuals [37], which may contribute to microvascular damage and cognitive decline [24].

We investigated the putative mechanistic link between central hemodynamics and cognitive function to determine whether cerebral and cerebrovascular remodeling and damage mediate the relation between aortic stiffness and memory. Mediating variables are intermediary variables that may provide a link between an observed (direct) effect between a predictor and an outcome. Quantifying how the mediator affects the observed relation may shine light onto possible pathological mechanisms [38–40]. To investigate the putative biological mechanism underlying the association between aortic stiffness and memory functional tests, we performed statistical mediation analysis [39]. Our analysis demonstrated that mechanisms involving cerebrovascular resistance and white matter hyperintensities (WMH) accounted for almost half of the observed relation between elevated CFPWV and lower performance on memory tests, whereas the direct relation between CFPWV and memory was no longer significant. Our results suggest that among older individuals, pathways that include cerebral microvascular remodeling and parenchymal damage contribute to the associations between elevated aortic stiffness and memory. It is important to acknowledge that in the forgoing study, we employed both a cross-sectional design and statistical mediation, which limits our ability to establish temporal and causal relations between CFPWV, mediators, and memory. In addition, since several other mechanisms may lead to cerebral SVD among the elderly, aortic stiffness may be sufficient but not necessary for the development of subclinical disease and cognitive impairment.

Perspectives

Recent findings suggest that vascular factors are potential targets for the prevention of memory impairment and AD. Without adequate autoregulation or compensatory remodeling to dampen pulsatile energy, elevated aortic stiffness transmits excessive pressure and flow pulsatility into the aging brain. Once this pulsatile energy penetrates into the cerebral microcirculation, microvascular damage, remodeling, and rarefaction may contribute to downstream ischemia and parenchymal damage. We and others have posited that this detrimental phenomenon targets deep brain structures, such as white matter and basal ganglia of the thalamus. These tissues are more susceptible to excessive pulsatility as they are perfused by short, penetrating branches that arise directly from the basilar or internal carotid arteries via the circle of Willis. In contrast to the long, circuitous muscular arteries that comprise the pial arterial network, these deep penetrating vessels provide minimal damping of the pulsatile pressure and flow that enters from large conduit vessels. Thus, structures perfused by these short, deep penetrators are more vulnerable to pressure and flow pulsatility and, hence, to abnormalities in aortic stiffness and pulsatile central hemodynamic load. On the other hand, the cerebral cortex is somewhat more protected as it is perfused by the circuitous and highly branched pial arteries, which attenuate pressure and flow pulsatility prior to their arrival in downstream tissues of the cerebral cortex. Indeed, we have shown that elevated CFPWV was associated with an increased prevalence of subcortical infarcts but not cortical infarcts [9, 24]. We have not examined an association of CFPWV with hippocampal structure; however, a recent study by Tarumi et al. [41] showed lower hippocampal and deep white matter

Fig. 1. Conceptual model based on the collective evidence showing how aortic stiffness contributes to cognitive impairment and incident neurological disease. CVR = Cerebrovascular resistance.

perfusion in individuals with elevated aortic stiffness. Since elderly individuals have blunted cerebral perfusion, an additional reduction of the cerebral blood flow due to cerebrovascular remodeling and impaired autoregulation may increase the risk for AD [42]. In addition to chronic hypoperfusion, pulsatile damage to small vessels in the brain may reduce the clearance of amyloid and tau proteins from the brain, possibly contributing to cerebral amyloid angiopathy and other protein clearance disorders associated with Alzheimer-type dementias [43]. Among middle-aged men, Shah et al. [44] showed that the β -amyloid-related risk for AD was higher with elevated diastolic blood pressure. In a study of elderly individuals without dementia, higher arterial stiffness and blood pressure were associated with higher β -amyloid deposition and more severe subclinical SVD [45]. Subsequently, Hughes et al. [46] showed that elevated arterial stiffness was related to progressive β -amyloid deposition in the brain of nondemented elderly adults over 2 years. In addition, Bangen et al. [47] revealed that the most common forms of cerebrovascular remodeling among patients with AD were atherosclerosis at the circle of Willis and arteriosclerosis. These data emphasize that remodeling of the aorta, elevated central hemodynamic load, and the subsequent damage and dysfunction of intracranial vessels convey a cumulative effect on brain structure and function that contribute to dementias, including AD, with advancing age.

Figure 1 depicts a conceptual model showing how aortic stiffness may give rise to cognitive impairment and incident neurological disease. Structural evidence of subclinical SVD may be assessed with brain magnetic resonance imaging (MRI) and manifests as reduced brain volume and an increased burden of cerebral infarcts, WMH, lacunar infarcts, enlargement of the perivascular space, and compromised flow through the basilar and internal carotid arteries [1, 48]. In addition, functional deficits associated with subclinical neurologic disease can be assessed by neuropsychological testing, which may reveal memory impairment – a precursor of dementia, including AD [7, 8, 49]. However, a crucial translational issue exists as to our ability to detect early-stage, subclinical cerebral SVD relatively quickly and at a reasonable cost in the clinic. Aortic stiffness, indicated by CFPWV, correlates with MRI

markers of subclinical microvascular dysfunction and can be measured easily in the clinic noninvasively. However, the utility of CFPWV alone for the detection of early-stage cerebral SVD is likely insufficient. We posit that CFPWV, along with other vascular and nonvascular factors, could be a component of a comprehensive risk assessment tool that would be sensitive enough to stratify patients on increasing cerebral SVD risk. Additional preventative strategies for individuals at higher risk may include evaluation and monitoring via MRI and cognitive examinations, which are more expensive and time consuming. In light of an ever-growing chorus of physiological and epidemiological data linking aortic stiffness to cognitive impairment, screening for cognitive decline among middle-aged individuals who have elevated CVD risk along with prevalent elevated aortic stiffness may be advisable [50].

Since subtler alterations in vascular function may occur before midlife, when the transition to accelerated aortic stiffening occurs [16], additional studies using a broad range of participants are needed in order to establish whether associations between aortic stiffness and memory are modified by age. Further studies to characterize the neurocognitive consequences of higher aortic stiffness and secondary microvascular brain damage are also warranted. Currently, no thorough examination of the effects of increased aortic stiffness and excessive pressure and flow pulsatility on global and regional brain blood flow and cognitive function exists. Recently, aortic stiffness was shown to be independently associated with orthostatic hypotension in a sample of older participants of the Rotterdam Study [5]. In light of the foregoing relations between aortic stiffness and impaired microvascular reactivity, individuals with a stiffened aorta also may be susceptible to adverse consequences of orthostatic hypotension. However, relations of orthostatic changes in blood pressure with brain structure and function have not been studied thoroughly. Identifying additional vascular factors that contribute to early alterations to brain integrity may lead to preventable measures before the manifestation of symptomatic cognitive impairment. Since the role of aortic stiffness in the putative associations between orthostatic changes in blood pressure and brain structure and memory function remains unknown, assessment of the interrelations of orthostatic blood pressure change, aortic stiffness, and brain structure and function is merited.

Conclusion

Vascular factors, including elevated aortic stiffness and microvascular dysfunction, contribute to memory impairment. The prevalence of vascular risk factors and subclinical disease is rising as the population ages, and unfortunately, these risk factors often remain undiagnosed or untreated as they are asymptomatic [51]. Fortunately, vascular factors are modifiable targets. Because of competing risks in older people, it is possible that only a modest reduction in vascular dysfunction and an associated delay in onset of cognitive impairment could markedly reduce the prevalence of dementia. Since current therapies to treat advanced neurocognitive impairment and neurodegeneration are relatively ineffective, interventions designed to modify vascular factors that focus on large-vessel and cerebrovascular function may represent a critical opportunity to prevent or delay memory impairment and the onset of AD.

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