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REVIEW

Cerebral hemodynamics and the aging brain

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Abstract

Aging is associated with a number of degenerative changes in the structure and function of blood vessels. Recent studies have examined the impact of age on cerebral hemodynamics and brain structure and function. These studies have shown age related changes in resting cerebral blood flow, cerebral vasoreactivity, cerebral autoregulation, and neurovascular coupling. Studies have also shown that aging is associated with cortical atrophy and cerebral white matter injury. More recent studies have also examined the relationship between age related cerebral hemodynamics and brain structure and function. Cross-sectional studies have shown that both cerebral vasoreactivity and pulsatility index are associated with cerebral white matter injury. Similarly, cerebral vasoreactivity has also been associated with impaired mobility which is known to be a clinical consequence of cerebral white matter injury in the elderly people. Neurovascular coupling has also been associated with slow gait and impaired executive function.

Despite the advances in this field, our understanding of the relationship between cerebral hemodynamics and structural changes in the aging brain is limited. We also know very little about the relationship between cerebral hemodynamics and clinical outcomes of structural brain disease. A better understanding of these relationships is an essential step towards identifying therapeutic targets and preventive strategies for age related cerebrovascular disease. This review summarizes the available data from recent studies examining cerebral hemodynamics and the aging brain.

Keywords: Cerebral hemodynamics, Aging brain, Cerebrovascular disease, Cerebral vasoreactivity, Cerebral autoregulation, Neurovascular coupling, White matter lesions, Cognitive impairment, Cerebral blood flow.

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Introduction

Aging is a leading risk factor for vascular disease. Even in the absence of traditional vascular risk factors such as hypertension, diabetes, or hyperlipidemia, vascular dysfunction is a nearly universal complement to advancing age [1]. Age related alterations in cellular homeostasis contribute to vascular remodeling, oxidative stress, and pro-atherogenic changes in the blood vessels.

Cerebrovascular aging is particularly relevant to functional disability in old age. Aging is associated with changes in regulation of cerebral blood flow (CBF), which may threaten cerebral perfusion and ultimately affect activities of daily living as a result of ischemia, syncope, falls, and cognitive impairments. The cerebrovascular system undergoes multiple changes throughout the human lifespan, probably beginning as early as the fourth decade in life [2].

This review summarizes the overall systemic structural and physiological changes related to vascular aging, with a special emphasis on the cerebrovascular system and ensuing age related declines in motor and cognitive function.

Structural changes associated with systemic vascular aging

Aging is associated with several structural changes in the vascular tree; the large conduit arteries become elongated and tortuous, the arterial lumen size increases and the arterial walls thicken. In addition, there is increased calcium deposition and collagen content in the intimal and medial layers with increased elastin fragmentation and thinning [3]. Accumulation of advanced glycation end (AGE) products from nonenzymation reaction of glucose with proteins, lipids, and nucleic acids leads to loss of vascular elasticity. Accumulation of the stiffer AGE-linked dysfunctional collagen results in increased collagen to elastin ratio and the mechanical stress on the vessel wall is borne by the collagen instead of the elastin. The age-related upregulation of tissue renin-angiotensin system is also linked to increased migration capacity of vascular smooth muscle cells and thickening of the vascular wall [4]. Overall, these age-related changes lead to stiffening of the arterial tree.

Aging is also associated with microvascular damage and rarefaction. Reduced vascular response to ischemic insults results in increased apoptotic endothelial cell death and impaired angiogenesis. Failure of normal activation of hypoxia-inducible factor-1α (HIF-1α) with aging leads to reduced trafficking of endothelial progenitor cells (EPC) to sites of ischemia as well as reduced expression of vascular endothelial growth factor (VEGF) and insulin like growth factor (IGF-1). Attenuation of IGF-1 further diminishes EPC survival and cell growth.

Irreversible changes at cellular level also play a role in vascular aging. Gradual age-related telomere attrition is associated with arrested cell proliferation [5]. Age related decline in stem cell number and function is also thought to lead to impaired vascular homeostasis and loss of repair capacity of the vascular system culminating in age-related atherosclerosis and progression of vascular disease [5]. Another factor known to decline with age is Sirtuin-1 (SIRT-1), which regulates the anti-aging signaling network. SIRT-1 exerts beneficial effects on the vasculature by promoting endothelium-dependent vascular relaxation, endothelial proliferation, and neovascularization. These age related process synergize, overlap, interact, and accumulate to alter the structure and function of the vascular system [5].

Physiological changes associated with systemic vascular aging

Aging is associated with endothelial dysfunction as a result of increased oxidative stress and reduced bioavailability of nitric oxide (NO) [6]. Therefore, blood flow in response to increased metabolic demand of the tissue is compromised. Flow-mediated vasodilatation (FMD) of the brachial artery following vascular occlusion is indicative of endothelium dependent vasodilatation. A reduction in FMD accompanied by elevated oxidative stress was observed in elderly individuals [7]. Oxidative stress is also implicated in cellular signaling pathways causing platelet aggregation, cell adhesion and inflammation in the vasculature. Normal aging is also associated with upregulation of pro-inflammatory vascular gene expression profile and increased plasma concentrations of inflammatory markers, which contribute to vascular dysfunction, endothelial apoptosis, and development of atherosclerosis [8].

Stiffening of the conduit arteries with age increases the aortic pulse wave velocity (PWV). As a result, systolic blood pressure is augmented and diastolic pressure is decreased, which leads to a widened pulse pressure. Augmentation of PWV and increases in pulse pressure is linked to increased collagen deposition, fibrosis, and intimal and medial thickening. These vascular changes result in ventricular hypertrophy due to increased workload of the heart and transmit higher pressure and higher flow pulsatility to the end organs, eventually causing adverse cardio- and cerebrovascular events [3].

Structural changes in the cerebral vessels

Several alterations across the entire cerebrovascular tree occur with age. Arterioles in the deep white matter regions become tortuous and with increasing vascular tortuosity, CBF becomes perfusion-dependent, leaving these deep white matter regions vulnerable to chronic hypoperfusion [9]. Periventricular venous collagenosis is also evident with aging. These changes result in narrowing or even occlusion of the lumen resulting in chronic ischemia and/or edema in the deep brain white matter regions. Similar to the systemic vessels, reduced activation of HIF-1α and VEGF expression also result in age related decline in ce-

rebral angiogenesis and hypoxic-ischemic response. Capillaries also undergo degeneration, loss of endothelium and thickening of the basement membrane with age. Animal studies have reported decreases in capillary number and density and increased inter-capillary distance with age [9]. The pericytes in the capillaries also undergo degeneration which mediates ischemic damage to the brain vessels by reducing CBF response during brain activation. Accumulations of neurotoxins occur following breakdown of the blood brain barrier [10]. Vessels in the cerebral gray matter also undergo similar structural changes with substantial rarefaction of the cerebral arterioles, decline in capillary density, thickening and fibrosis in and around the basement membrane of these vessels.

Physiological changes in the cerebral vessels

Cerebral blood flow

Advancing age is associated with a decline in resting CBF. Several studies utilizing transcranial Doppler (TCD) ultrasonography and functional imaging techniques have consistently reported a decrease in blood flow velocity through major cerebral arteries and a decline in regional cerebral perfusion with aging [2, 11]. CBF in the cerebral cortex and the basal forebrain has been found to be consistently lower with age. However, the underlying mechanism for this decrease is unknown. Age related atrophy in cerebral volume and microvascular rarefaction may contribute to the decline in CBF. Alternatively, the decrease in CBF in the aged brain could be a secondary effect of attenuation in neural activation and a shift towards lower cerebral metabolic activity rather than a primary factor contributing to the decline in neural activation [12].

Cerebral vasoreactivity

Cerebral vasoreactivity (VR) to various stimuli such as changes in end-tidal carbon dioxide (CO_2) or drugs is used to assess cerebral perfusion reserve. Cerebral VR, which is a NO-dependent process, is also considered a measure of endothelial function in the cerebral arteries [13-15]. The impact of age on cerebral VR is controversial. Some studies have reported a decline in VR with age [11]. In the Rotterdam study, VR declined at a rate of 0.6%/kPa per year with increasing age up to 90 years, though data was scarce for the advanced age population. Sex-related differences in VR have also been reported with aging. Age related reduction in VR was seen in postmenopausal women, but not in men, suggesting possible hormonal influences affecting VR [16]. Age related differences in regional cerebral vascular response to changes in end-tidal CO_2 have also been reported using positron emission tomography [14]. Vasodilatation in the cerebellum and insular cortex during hypercapnia and vasoconstriction in the frontal cortex during hypocapnia was greater in the younger subjects compared to the older subjects, suggesting less effective vascular response in cerebral perforating arteries, possibly as a result of arteriosclerosis with normal aging. Utilizing blood oxygenation level-dependent (BOLD) functional MRI during a dual task of global hypercapnic breath-holding and finger tapping task in young and old subjects, mean BOLD signal amplitudes were significantly smaller in the older subjects, again suggesting age related decline in VR to vasodilatory stimulus despite similar neuronal activation [17].

Dynamic Cerebral Autoregulation

Dynamic cerebral autoregulation (dCA) is the intrinsic property of the cerebral vessels to maintain flow despite rapid changes in systemic pressure. Many studies have been conducted to assess dCA in normal aging [18]. While different measurement conditions, protocols, and assessment techniques were used, the conclusions were similar. In one study dCA assessed with frequency domain transfer function analysis during steady state sitting and standing was shown to be preserved in the elderly subjects [19]. Another study, utilizing the time domain correlation index between spontaneous changes in blood pressure and CBF velocity, also reported no differences in dCA between young and old subjects [20]. Carey et al. estimated autoregulatory index from dynamic pressure stimulus using lower body negative pressure and Valsalva maneuver and depressor stimulus using bilateral thigh cuff inflation and also showed that dCA was unaffected by aging [21]. While all these studies conclude that aging is not associated with a decline in dCA, it is important to note that the age range of the subjects in these studies varied between 50-75 years. Therefore, the impact of advanced age (>75 years) on dCA is unknown.

Pulsatility index

Pulsatility index (PI), which measures cerebrovascular compliance, is calculated from the CBF velocity as the difference between systolic and diastolic flow velocities divided by the mean flow velocity [18]. Higher PI is reflective of lower cerebrovascular compliance. The percent change in PI measured during a dynamic exercise study was similar between the young and older subjects with a delay in response to PI in the older group suggesting less influence of exercise-induced sympathetic activity in cerebral vasculature of the older subjects [22]. Another study measuring PI during lower body negative pressure induced orthostasis in physically unfit and fit young and old subjects reported that PI was not influenced by either age or fitness level [23]. However, in both these studies blood pressure was monitored once every minute which might have confounded the results.

Neurovascular coupling

Neurovascular coupling (NVC) or functional hyperemia is measure of close spatial and functional relationship between neural activation and CBF. NVC ensures that blood flow is increased to meet the increased metabolic demands of the activated neurons [15]. A mismatch between the de-

mand and supply would result in relative hypoperfusion and brain dysfunction. A study using functional TCD measurements during a visual stimulation in subjects ranging from 10–60 years did not find any age-related difference in visual activation-induced CBF velocity changes, suggesting that NVC is unaffected by aging [24]. In another study involving young and old subjects, functional TCD was used to assess NVC in the anterior and posterior cerebral arteries during visual and executive function tasks to activate the occipital and frontal lobes, respectively [25]. While the younger group showed task specific flow activation in either territory, the older group showed a generalized increase in blood flow in both the territories in response to both tasks, suggesting generalization of cerebral activity to compensate for age-related loss of region specific function. Similar generalization of cerebral activity was also reported with functional MRI during cognitive tasks in elderly people [26]. Overall NVC seems to be altered with aging.

Clinical manifestations of hemodynamic changes with aging

Cerebral small vessel disease, manifested by white matter hyperintensities (WMH) on brain magnetic resonance imaging (MRI), is a common finding in elderly individuals. These MRI findings, which consist of areas of increased brightness and appear as punctate or confluent patches in deep subcortical white matter tracts, particularly those close to the ventricles, have been associated with impairments in cognition and physical function in the elderly people [15]. With normal aging, WMH progress by about 44% in the deep and 30% in the periventricular white matter over a 3 year period with greatest progression seen in the frontal region [27]. The suggested mechanisms underlying WMH include chronic ischemia, hypoperfusion due to endothelial dysfunction and impaired cerebral autoregulation, increased pulsatility of the cerebral vessels as a result of arterial stiffening, blood brain barrier leakage, edema, inflammation, and degeneration [15, 28]. Histopathological correlates of WMH include cortical atrophy, loss of myelinated fibers and axonal disruption. WMH typically accumulate in regions supplied by direct penetrating branches of the cerebral circulation which are susceptible to increased flow pulsatility and increased pressure due to wave reflection. In support of the hypoxic-ischemic mechanism, increased levels of protein markers of hypoxia have also been associated with the prevalence of WMH in a cohort of elderly people [15].

The link between WMH and clinical outcomes such as physical function and cognition has been demonstrated in a number of studies. In a multi-center LADIS study, WMH was shown to be an independent determinant of transition to disability in subjects between 65–84 years [29]. Decline in gait, walking speed and balance performances were directly correlated with the severity of WMH. Similar findings were also reported by investigators examining gait variables using a composite score [30]. In this study, subjects with poor gait scores and higher occurrences of falls were shown to have greater volumes of WMH. Another group observed that WMH, predominantly in the centrum semiovale and periventricular frontal regions, were associated with lower gait speed, shorter stride length, and broader stride width [31]. They also utilized diffusion tensor imaging to examine the microstructural integrity of normal-appearing white matter and demonstrated that in elderly subjects with WMH, there was widespread disruption in white matter microstructural integrity as indicated by a lower fractional anisotropy and higher mean diffusivity. Disrupted normal white matter microstructural integrity was associated with impaired gait measures. Similar relationships between brain structure and cognition have also been observed with aging. Individuals with better cognition as demonstrated by better performance on executive tasks also had lower volume of WMH in the frontal brain regions [32]. Increased WMH burden predicted poor performance on cognitive task involving executive function and processing speed. Among healthy older adults, individuals with poor cognition especially in the executive domain have also been shown to be more prone to falls [33]. Although the etiology of age related WMH is yet to be established, several studies have highlighted the relationship between the hemodynamic changes and clinical manifestations of WMH on the aging brain. These studies are summarized below.

Cerebral blood flow

Gradual decline in CBF over time is linked to increased risk of developing WMH. In a population based study using TCD and MRI in 628 elderly individuals WMH was strongly associated with low CBF velocity [34]. This study reported a fourfold increase in the risk of severe WMH in subjects with low CBF velocity in the middle cerebral artery compared to subjects with high CBF velocity. Decline in CBF velocity emerged to be a stronger risk factor for the presence of WMH than age and high blood pressure in this population. Another study utilizing arterial spin labeling to measure regional CBF reported that CBF was lower in areas of WMH relative to normal appearing white matter in healthy older individuals [35].

Pulse wave velocity and pulsatility index

In a community based cohort of elderly people ranging between 69–93 years, increased carotid PI and carotid-femoral PWV were both related to increased risk of subcortical infarcts with a hazard ratio of 1.62 and 1.71 per standard deviation, respectively [36]. Carotid femoral PWV was also associated with higher WMH volume and carotid PI was associated with lower whole brain grey and white matter volumes. Both these hemodynamic indices were also associated with lower scores in multiple cognitive domains. Similar relationships between middle cerebral artery PI and severity of WMH volumes have also been reported in

a community dwelling group of elderly subjects [37]. It has been hypothesized that aortic stiffness exposes the cerebral microcirculation to abnormal physical forces marked with increased PWV and increased transmission of flow pulsatility to the brain causing microvascular remodeling and ischemic damage to the brain and leading to clinical manifestations of cognitive impairment [38].

Dynamic cerebral autoregulation

Animal models provide evidence that cerebrovascular dysfunction and vascular changes are key contributors to hypoperfusion and eventually result in white matter damage. In animal models of small vessel diseases, impaired cerebral autoregulation is apparent months before the first evidence of white matter damage [39]. In a cross-sectional study of elderly individuals with vascular risk factors, we found that higher WMH volumes and lower microstructural integrity (lower fractional anisotropy and higher mean diffusivity) of the white matter was associated with less effective dCA [40].

Cerebral vasoreactivity and flow mediated dilatation

WMH are associated with decline in systemic and cerebrovascular endothelial function. In older adults with cardiovascular risk factors, FMD measured in the brachial artery was inversely associated with WMH volume [41]. In elderly subjects from the population-based Rotterdam study, cerebral VR to changes in end-tidal CO_2 was found to be inversely associated with deep subcortical and total periventricular WMH [42]. The most robust relationship was between impaired cerebral VR and periventricular WMH which is a watershed territory in the brain, suggesting that hypoperfusion and subsequent ischemia in these regions may be the causal mechanism leading to WMH. Cerebral VR on the other hand has also been associated with impaired mobility in the elderly people. In 419 community dwelling individuals from the MOBILIZE Boston Study, Cerebral VR was linked to gait speed. Subjects in the lowest quintile of VR had lower gait speeds compared to those in the highest quintile. Also, subjects in the highest quintile of VR had significantly lower fall rates [43].

Neurovascular coupling

NVC has also been linked to WMH and clinical outcomes in the elderly people. Data from the MOBILIZE Boston study, show that changes in CBF velocity responses to an N-Back task (referred to as NVC) was significantly associated with gait speed and that subjects with higher NVC were able to suppress the negative relationship between WMH and gait speed [44]. In other words, individuals with faster gait speed despite increased WMH burden also exhibited higher NVC. In another study involving older individuals, impaired NVC was associated with poor executive function as measured by the Trails making test B [45]. Moreover, higher NVC coupling was associated with greater white matter microstructural integrity as measured by diffusion tensor imaging.

Summary

Age related changes in the structure and function of the system and cerebral vascular tree have been demonstrated in many studies. A number of age related structural changes in the brain, which clinically manifest with cognitive and mobility impairment, have also been linked to vascular mechanisms. **Figure 1** provides an overview of the relationship between cerebrovascular aging and clinical outcomes.

Future longitudinal studies linking specific age related vascular changes to brain structural changes and age related mobility and cognitive impairment will help identify therapeutic targets for the prevention and treatment of vascular causes of these disorders.

Abbreviations

AGE: Advanced glycation end; BOLD: Blood oxygenation level-dependent; CBF: Cerebral blood flow; CO_2: Carbon dioxide; dCA: Dynamic cerebral autoregulation; EPC: Endothelial progenitor cells; FMD: Flow-mediated vasodilatation; HIF-1α: Hypoxia-inducible factor-1α; IGF-1: Insulin like growth factor; MRI: Magnetic resonance imaging; NO: Nitric oxide; NVC: Neurovascular coupling; PI: Pulsatility index; PWV: Pulse wave velocity; SIRT-1: Sirtuin-1; TCD: Transcranial Doppler; WMH: White matter hyperintensities; VEGF: Vascular endothelial growth factor; VR: Vasoreactivity

Competing interests

The authors declare no conflict of interest.

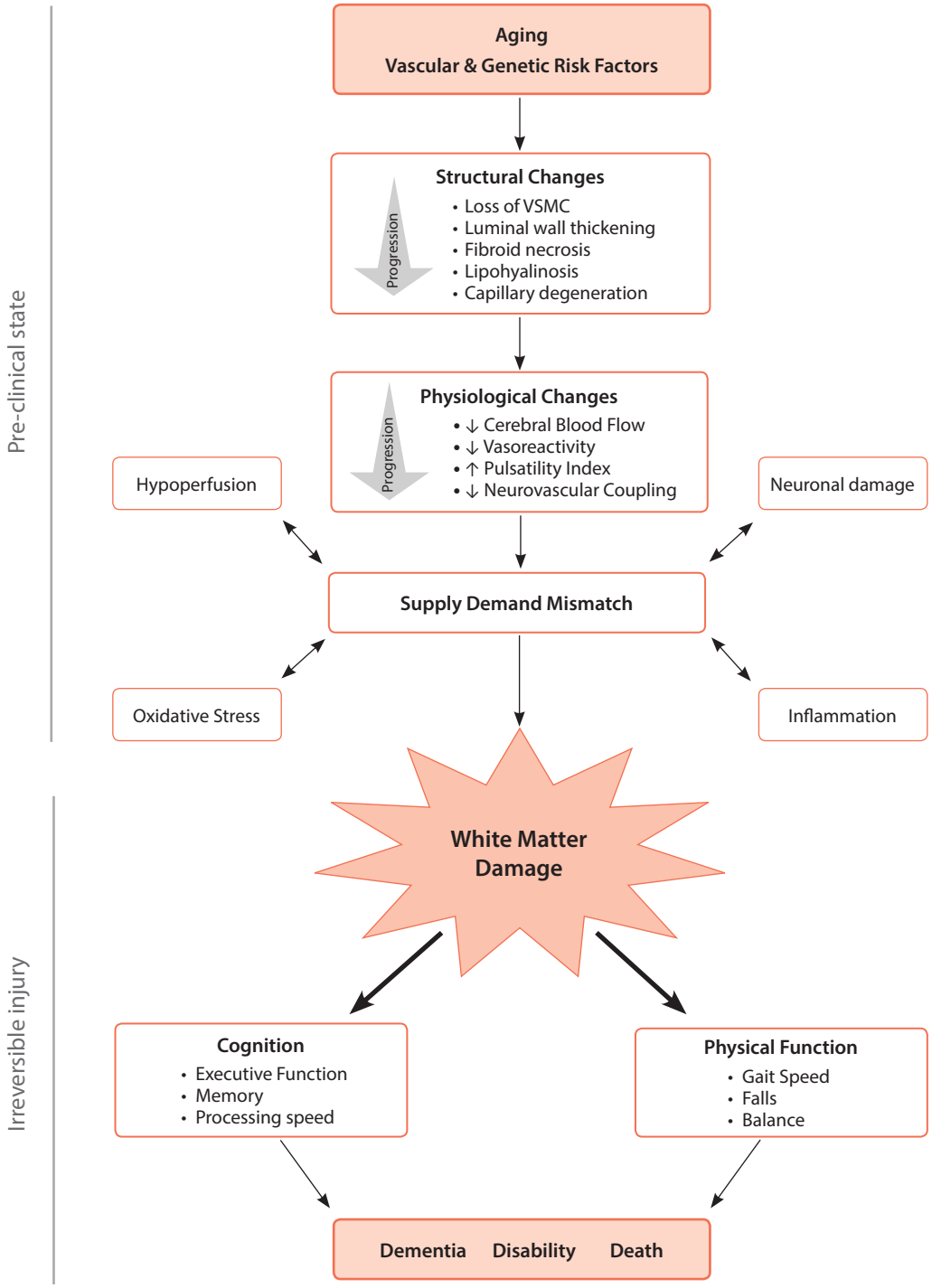

Figure 1. Relationship between cerebrovascular aging and clinical outcomes.

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