Correia *et al. Artery Research* (2025) 31:17
https://doi.org/10.1007/s44200-025-00085-9

Artery Research

REVIEW ARTICLE

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Intracranial Pressure and Vascular Aging: A Narrative Review on its Role in Monitoring Cognitive Decline

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Abstract

Vascular aging is closely associated with the development of cardiovascular disease and cognitive impairment and is a determining factor in overall morbidity and mortality. The continued presence of modifiable risk factors, such as hypertension, diabetes mellitus, obesity, and a sedentary lifestyle, accelerates this process and contributes to its complications. In this context, arteriosclerosis and atherosclerosis play a central role in the loss of arterial elasticity, increasing susceptibility to cardiovascular and cerebrovascular events. Arterial stiffness, measured by pulse wave velocity, has been correlated with the risk of dementia and cognitive decline, highlighting the need for early intervention. In addition, monitoring intracranial pressure has emerged as a potential biomarker for assessing the impact of vascular aging on the brain, helping to preserve brain integrity and prevent cognitive impairment. In this narrative review, we discuss the pathophysiological mechanisms of vascular aging and their relationship with pulse wave velocity, as well as explore intracranial pressure monitoring as a possible marker for the progression of cerebral vascular aging and its impact on cognitive function.

Keywords Vascular stiffness, Cardiovascular diseases, Arterial stiffness, Cerebrovascular disorders, Cerebral arterial disease, Cognitive dysfunction, Hypertension, Intracranial pressure, Pulse wave velocity

1 Background

In an aging population scene, cardiovascular disease (CVD) compromises the quality of life of millions of people [1]. The relationship between cardiovascular disease and vascular aging is complex and multifaceted, involving processes such as arteriosclerosis and atherosclerosis, which promote progressive damage to arterial structure and function [2]. These alterations not only contribute to the occurrence of cardiovascular outcomes but also play a central role in the development of cognitive decline and dementia, conditions of increasing global relevance [3, 4].

Despite advances in understanding the pathophysiological mechanism of CVD, important gaps remain, especially regarding the early identification and management of accelerated vascular aging (AVA). Recent studies suggest that early interventions may offer a unique opportunity to prevent cardiovascular and neurological complications in the medium and long term [5, 6].

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During vascular aging, arteries lose elasticity and become stiffer, and this arterial stiffening can be quantified by pulse wave velocity (PWV). Increased PWV reflects systemic arterial stiffness, which can compromise cerebral autoregulation and intensify pulsatile flow in the cerebral microcirculation [7, 8]. These changes can reduce intracranial compliance, although the relationship between arterial stiffness and intracranial pressure (ICP) is still under investigation. Increased ICP, in turn, decreases cerebral perfusion pressure, favoring the development of neurological dysfunctions, including cognitive impairment and vascular dementia [9]. In addition, evidence indicates that increased PWV may be associated with reduced cerebral blood flow and worsened cognitive performance, especially in areas such as memory and executive functions [10–13].

The recent ability to non-invasively monitor intracranial compliance it possible to use it as a cerebral vital sign, supporting its potential as a biomarker for vascular brain aging and related structural damage. In light of this, the aim of this review was to explore the mechanism underlying vascular aging and its relationship with pulse wave velocity, as well as to explore ICP monitoring as a possible biomarker for the progress of cerebral vascular aging and its impact on cognitive function. By addressing cardiovascular risk factors, cardiovascular risk biomarkers, and potential cardiovascular assessment strategies, we aim to contribute to a better understanding of the possibilities that permeate prevention and treatment, mitigating the impacts of CVD on global health.

2 Methods

A narrative approach was used in this review, allowing for a synthesis of relevant evidence on the relationship between vascular aging, pulse wave velocity, cognitive decline, and intracranial pressure. The information collected was organized systematically to build a cohesive and comprehensive narrative. The bibliographic search was carried out in the PubMed/MedLine, Scopus, and SciELO databases using the following descriptors: arterial hypertension, arterial stiffness, pulse wave velocity, aging, vascular aging, intracranial hypertension, intracranial pressure, cognitive decline, and cognition. Boolean operators (AND, OR, and NOT) were used to refine the results. Articles published up to December 2024 in English or Portuguese were included. In addition, a manual search was conducted in the reference lists of the selected studies to identify additional potentially relevant publications.

3 Main Text

3.1 Vascular Aging

3.1.1 Epidemiology

CVD continue to be the leading cause of death worldwide, producing significant morbidity and high costs for health services [14]. It is estimated that CVD are responsible for more than 40 million years lost due to disability each year, and this figure has doubled in the last two decades and may rise as a result of population growth and global aging [15].

Among the elderly population, CVD and cerebrovascular disease are the main causes of morbidity and disability. In addition to the impact of biological aging on age-related macrovascular diseases, the growing importance attributed to associated microvascular pathologies stands out [16]. Evidence suggests that up to 48% of dementias could be prevented by controlling risk factors [17]. Studies indicate that CVD subclinical lesions and cognitive decline begin decades before clinical events, offering a window for early interventions [5].

Identifying and treating Early Vascular Aging (EVA) is critical for primordial prevention. In. this context, it is important to understand this concept as the deterioration in arterial structure and function leading to damage of the heart, brain, kidney, and other organs. Many cardiovascular risk factors, along with genetic predisposition, can accelerate and promote EVA (Fig. 1)[18].

3.2 Physiopathology

3.2.1 Vascular Aging and the Process of Atherosclerosis

This process of vascular aging involves structural and functional changes in the artery wall, associated with arteriosclerosis and atherosclerosis mechanism [19]. While arteriosclerosis refers to the general stiffening and loss of elasticity of arteries and atherosclerosis involves the buildup of plaques within the arterial wall, physiological vascular aging encompasses both processes but can also occur independently as part of normal aging, even in the absence of overt cardiovascular disease.

In atherosclerosis, there is a predominant impairment on the medium tunic, characterized by the replacement of elastin fibers for collagen, destruction of muscle fibers, and calcium deposition. These changes lead to arterial stiffness, reducing the damping capacity of pulsatile blood flow and causing damage to target organs [2, 20]. Increased arterial stiffness mainly affects organs with higher blood flow demand and low resistance, such as the brain and kidneys, and can result in cerebral damage (cognitive impairment/dementia) and the progression of chronic kidney disease [21, 22].

In atherosclerosis, there is a progressive accumulation of inflammatory and immune cells, smooth muscle cells,

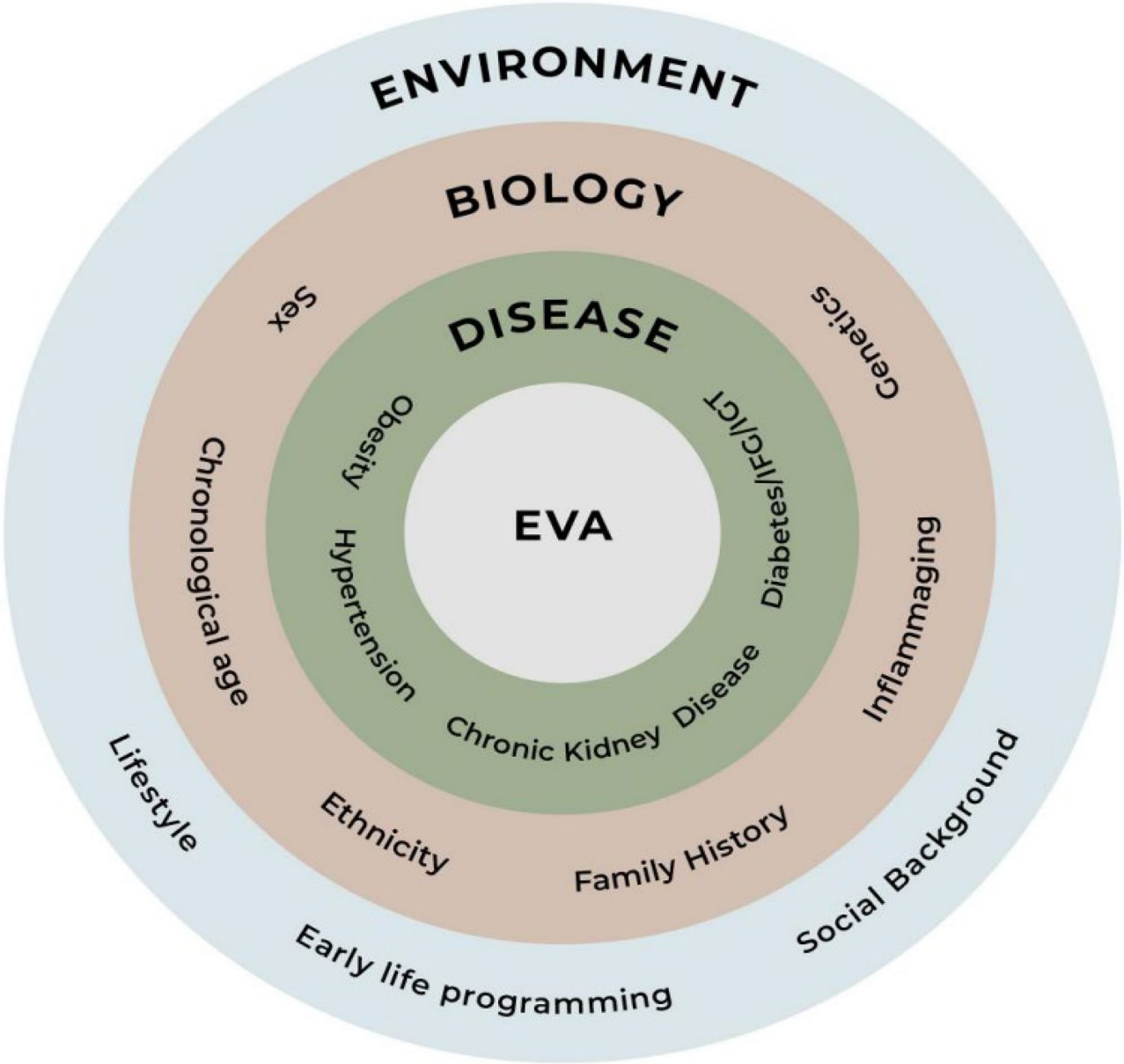

Fig. 1 Factors contributing to why some people display early EVA compared to others. *IFG* impaired fasting glucose, *IGT* impaired glucose tolerance. Source: Climie et al., 2023

lipids, and connective tissue in the intimal of medium and large-caliber arteries. This process leads to the narrowing of the arterial lumen and increased arterial stiffness, especially in the older and calcified atherosclerotic plaques, which in combination with local thrombotic phenomena result in clinical events [23].

Arteriosclerosis and atherosclerosis, although different, are linked anatomically and functionally [24, 25], often coexisting in a vicious cycle in which increased arterial stiffness precedes and promotes the progression of atherosclerosis [26–28].

Arterial stiffness analysis has been used as a tool to detect AVA early and identify individuals who are more susceptible to cardiovascular risk factors [29]. Early interventions and prevention strategies focused on risk factors can help to mitigate the effects of vascular stiffness triggered by AVA (Fig. 2) [6, 18].

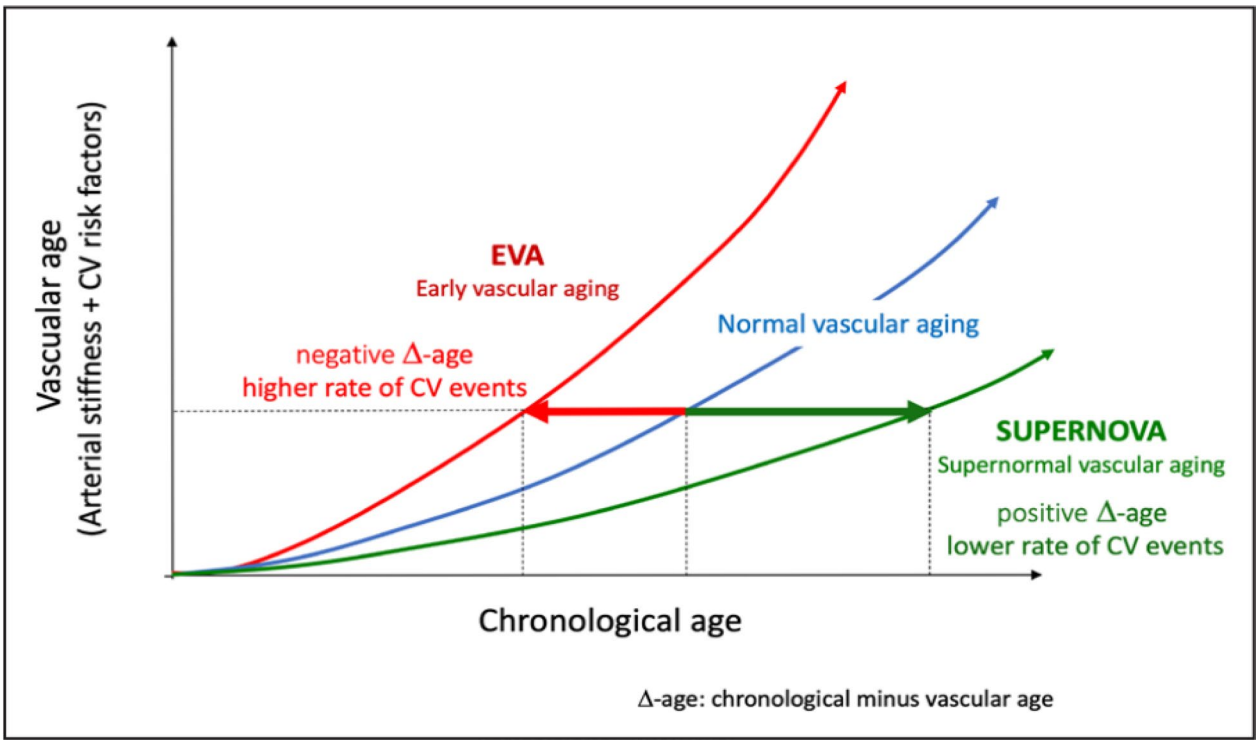

Fig. 2 Phenotypes of vascular aging. For a substantially similar vascular age and cardiovascular (CV) risk profile (solid arrows), EVA individuals are significantly younger and supernormal vascular aging (SUPERNOVA) are significantly older than the normal vascular aging (VA) aging group. As a consequence, SUPERNOVA subjects have the largest difference between chronological and vascular age (Δ-age,); conversely, EVA subjects have negative Δ-age. This translates into a lower rate of CV events in SUPERNOVA subjects, and a higher rate in EVA subjects; in other words, Δ-age is inversely associated with CV events. Source: Bruno et al (2020)

3.3 Risk Factors for Early Vascular Aging and Cardiovascular Disease

3.3.1 Non-modifiable

Genetic and epigenetic factors significantly influence the morbidity and mortality associated with CVD [30–33]. However, a meta-analysis with twins revealed that genetics is responsible for only 20–30% of the variability in life expectancy, indicating that environmental and behavioral factors play a predominant role in this process.

3.4 Modifiable

The environment influences vascular aging from the intrauterine period onwards, with the impact of the parents' lifestyle modifying the health of their offspring in the long term [34, 35].

Factors such as a balanced diet, physical exercise, smoking cessation, and alcohol control are essential for preventing CVD. Diets based on vegetables and unprocessed foods, such as the Mediterranean diet, are associated with healthy vascular aging [33]. Sedentarism is also a major risk factor, and even small amounts of exercise reduce CVD and mortality [36, 37].

Hypertension (HT) stands out as a crucial factor in increasing arterial stiffness [21]. It is suggested that an increase in blood pressure (BP) occurs to compensate for the deleterious effects of hypertrophy on the arterial wall [38]. The progressive increase in arterial stiffness with advancing age has been parallel to the increase in BP. If the increase in wall stress persists, as in the presence of HT, we will have remodeling arterial wall remodeling [39, 40].

In addition, growing evidence suggests that there is a vicious cycle between hyperglycemia, metabolic syndrome, and arterial stiffness, resulting in AVA in individuals with diabetes and metabolic syndrome [2, 20]. Furthermore, obesity influences measures of vascular age, including arterial stiffness and markers of inflammation, as well as representing a risk factor for type 2 diabetes, impacting increased CVD-related mortality [41], which is worrying given the obesity pandemic present in the world today [31].

Diseases with chronic inflammation (such as autoimmune disease) are known to accelerate the atherosclerosis process and are also associated with an accelerated arterial stiffening process [42].

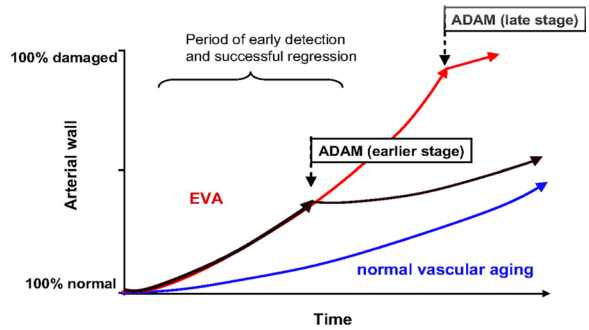

Fig. 3 Time course for the development of EVA and start of intervention with ADAM in patients at increased cardiovascular risk. Source: Nilsson, Boutouyrie, and Laurent (2009).

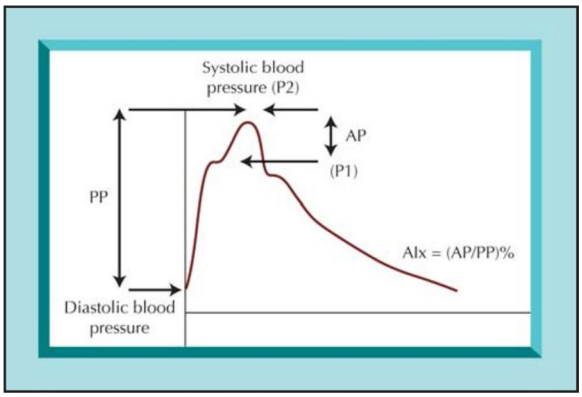

Fig. 4 Graph representing blood pressure curves and Augmentation index. Central blood pressure wave and calculation of the augmentation index (AIx). AIx is the ratio between augmented pressure (AP) and pulse pressure (PP). AP is the increase of systolic pressure due to the reflected wave; it is calculated as the difference between the second systolic peak (P2) and the first systolic peak (P1). [44] Source: Ghiadoni et al (2009)

Other factors that influence aging and longevity can also be mentioned, for example, air quality, household air pollution, quality and duration of sleep, physiological factors, and socioeconomic status [43–46].

3.5 Vascular Aging Phenotypes

Individual variability in vascular aging reflects differences in the mechanisms involved, leading to the concept of biological aging, which is distinct from chronological aging. While chronological aging refers only to the passage of time, biological aging is related to the decline of organic function. Individuals with EVA have more CVD risk and early mortality, while those with normal aging or supernormal aging (Fig. 2) tend to be longer-lived [47, 48]. Also important to understand the ADAM concept, meaning that adequate and early interventions may counteract the process involved in the EVA syndrome (fig. 3) [18].

Biomarkers that truly reflect the state of vascular aging are needed to improve the early detection of individuals at high risk of developing CVD. These must surpass chronological age as determinants of morbidity and mortality. In addition, their quantification must be easy, safe, and non-invasive [49].

3.6 Assessment Methods

When assessing arterial stiffness, the important variables are central systolic BP (cSBP), central pulse pressure (cPPP), Augmentation Index (Aix), and PWV.

cSBP is an indicator of left ventricular ejection pressure, with a proven association with future cardiovascular events [29, 37, 50]. PPc is the difference between PASc and central diastolic BP (cPAD), representing the pulsatile component of hemodynamics [51, 52]. The Aix represents the amplitude of the reflected wave, influenced by the stiffness of the small arteries. It is an alternative index derived from the analysis of the central aortic pressure curve and quantifies the effect of wave reflection, as shown in Fig. 4 [51–54].

PWV is a simple, non-invasive biomarker and can be considered the gold standard for measuring arterial stiffness and can be inferred as subclinical target organ damage associated with increased cardiovascular risk [55].

3.7 Pulse Wave Velocity

The PWV is a biomarker widely recognized for arterial stiffness and cardiovascular risk [56–58]. Studies indicate that carotid-femoral PWV values above 10 m/s or above the 90th percentile of the distribution are considered high-risk markers [59].

The PWV is measured using transducers placed on the skin at the prominence of the right common carotid artery and the right femoral artery. The device calculates the time interval between the start of the carotid wave and the start of the femoral wave, which using the measurement of the distance between the transducers then gives the aortic PWV.

Arterial stiffening causes the ejection of blood from the left ventricle (LV) to generate a pressure wave of greater amplitude in the aorta than in the LV, due to a decrease in aortic compliance. Another effect that can be observed is that with increased arterial stiffness there is an increase in the speed of pulse wave propagation through the aorta and large arteries [60].

In hypertensive patients, significant changes in the stiffness of the large arteries are observed, while the small cerebral vessels do not show such obvious structural changes [61]. Thus, the association between HT and brain damage is attributed to molecular, structural, and

mechanical factors that compromise the cerebral blood flow (CBF) autoregulation mechanism [62].

The reduction in the contractile capacity of cerebral vascular smooth muscle cells, often related to aging, results in an imbalance between perfusion pressure and cerebral vascular resistance. This phenomenon amplifies the transmission of pulsatile energy and favors the occurrence of microvascular injuries [8, 62].

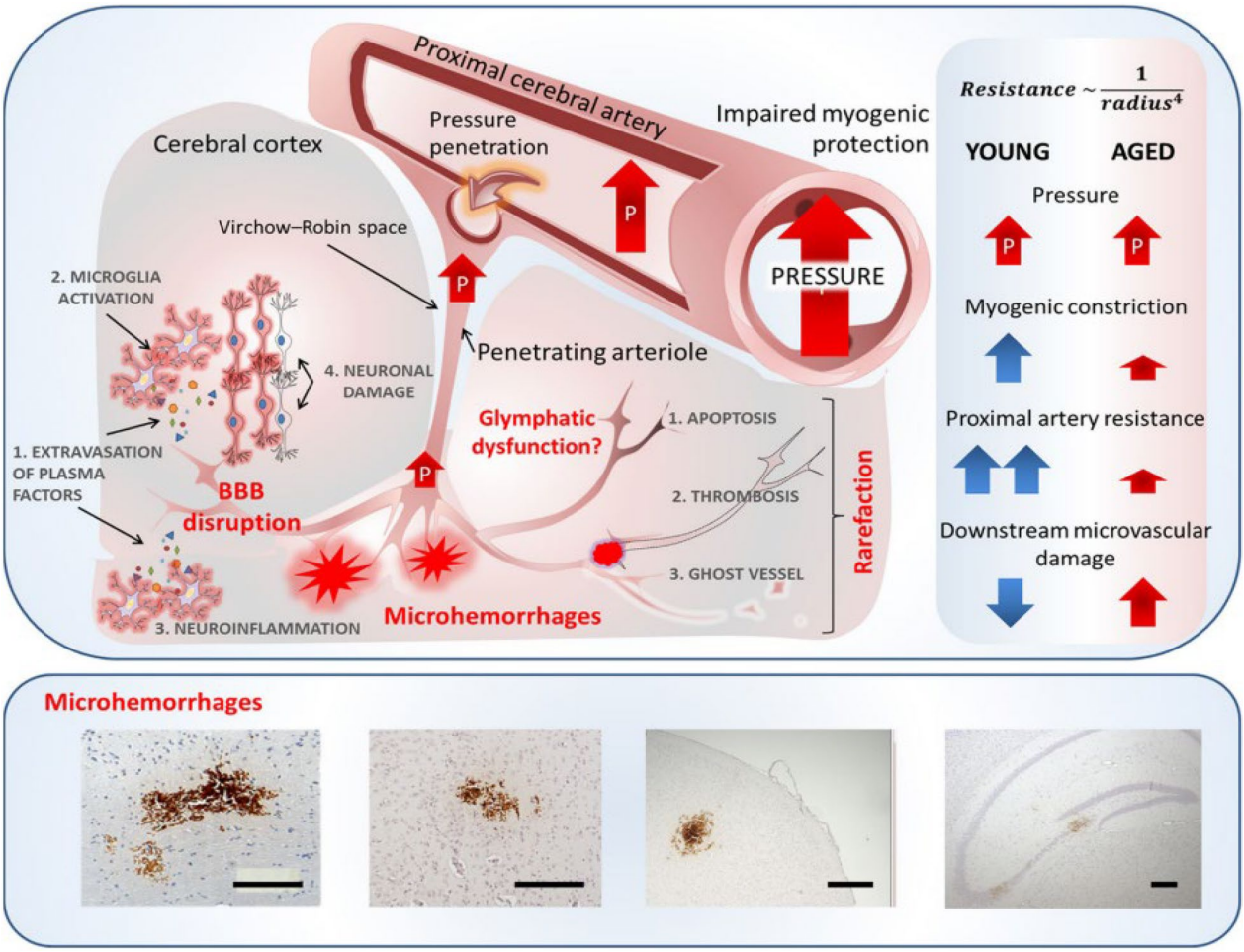

Fig. 5 Age-related autoregulatory dysfunction exacerbates hypertension-induced cerebromicrovascular injury. Shown is a schematic illustration of the likely consequences of autoregulatory dysfunction in the aging brain. The model proposed implies that in healthy young organisms pressure-induced myogenic constriction of the proximal cerebral arteries acts as a critical homeostatic mechanism that assures that increased arterial pressure does not penetrate the distal portion of the microcirculation and cause damage to the thin-walled arteriolar and capillary microvessels in the brain (103, 147). In aging, proximal resistance arteries lose their capability to adapt to hypertension with an enhanced pressure-induced constriction, which leads to a mismatch in perfusion pressure and segmental vascular resistance (resistance is inversely related to the 4th power of vessel radius). Lack of proper autoregulatory protection in aging likely allows high blood pressure to penetrate the vulnerable downstream portion of the cerebral microcirculation. The hemodynamic burden exacerbates age-related disruption of the blood–brain barrier (BBB), leading to extravasation of plasma factors, which promote neuroinflammation (e.g., activation of microglia by IgG via the IgG Fc receptors). Microglia-derived proinflammatory cytokines, chemokines, proteases [i.e., matrix metalloproteinase (MMP)], and reactive oxygen species (ROS) promote neuronal damage (273, 281). In addition, the increased microvascular pressure activates matrix metalloproteinases in the vascular wall in a redox-sensitive manner, contributing to the development of microhemorrhages (276). The age-related autoregulatory dysfunction and its consequences may also contribute to the dysfunction of the glymphatic system (128, 148), and the development of age-related vascular rarefaction (281). We posit that exacerbation of neuroinflammation, cerebral microhemorrhages, glymphatics dysfunction, and/or microvascular rarefaction are causally linked to hypertension-induced cognitive impairment in aging (85, 210, 285) and contribute to the increased prevalence of Alzheimer's disease in hypertensive elderly individuals. Bottom: representative images showing cerebral microhemorrhages (brown lesions after diaminobenzidine–hematoxylin staining, scale bar // 200 m) in the brain of aged (24-month old) hypertensive mice, which associate with autoregulatory dysfunction. Note that most hypertension-induced microhemorrhages are located in the cortical and subcortical region. Hypertension was induced in the mice by treatment with angiotensin II and the nitric oxide synthase inhibitor nitro-L-arginine methyl ester (L-NAME). [54] Source: Toth et al (2017)

Increased pulse pressure, characteristic of states of high arterial stiffness, is associated with mechanical stress on the cerebral microcirculation, exposing the brain parenchyma to a greater risk of injury (Fig. 5) [63]. Furthermore, in hypertensive patients, the BP variability correlates with worse cognitive performance, as observed in prospective studies with many years of follow-up [64, 65].

Evidence suggests that high PWV plays a crucial role in the development of brain lesions, such as lacunar infarcts (LI), microhemorrhages, and damage to cerebral white matter, as well as being associated with dementia and reduced cognitive function (Fig. 6) [21, 66–68].

Neuroimaging studies show that hypertensive patients with higher PWV have a greater extent of white matter and silent LI [69]. An analysis involving more than 7.000 individuals in the Framingham Study, with an average follow-up of 15 years, demonstrated that PWV has an independent predictive value for dementia, transient ischemic attack, and stroke [10]. Similarly, the Toledo Study for Healthy Aging identified a correlation between high PWV (baseline values of 13–18 m/s) and progressive worsening in cognitive performance after 3–4 years of follow-up [11].

A post hoc analysis of 8563 patients from SPRINT-MIND (Memory and Cognition in Decreased Hypertension) showed that the estimated PWV had an independent predictive value for cognitive alterations (probable dementia or mild cognitive impairment) in hypertensive patients. In addition, patients who responded to intensive treatment for HT (assessed by PWV) had a lower risk of cognitive alterations, suggesting that the PWV estimate could be used as a potential tool for assessing antihypertensive treatment [12].

Data from ELSA-Brazil (Longitudinal Study of Adult Health) also reinforces the impact of high baseline

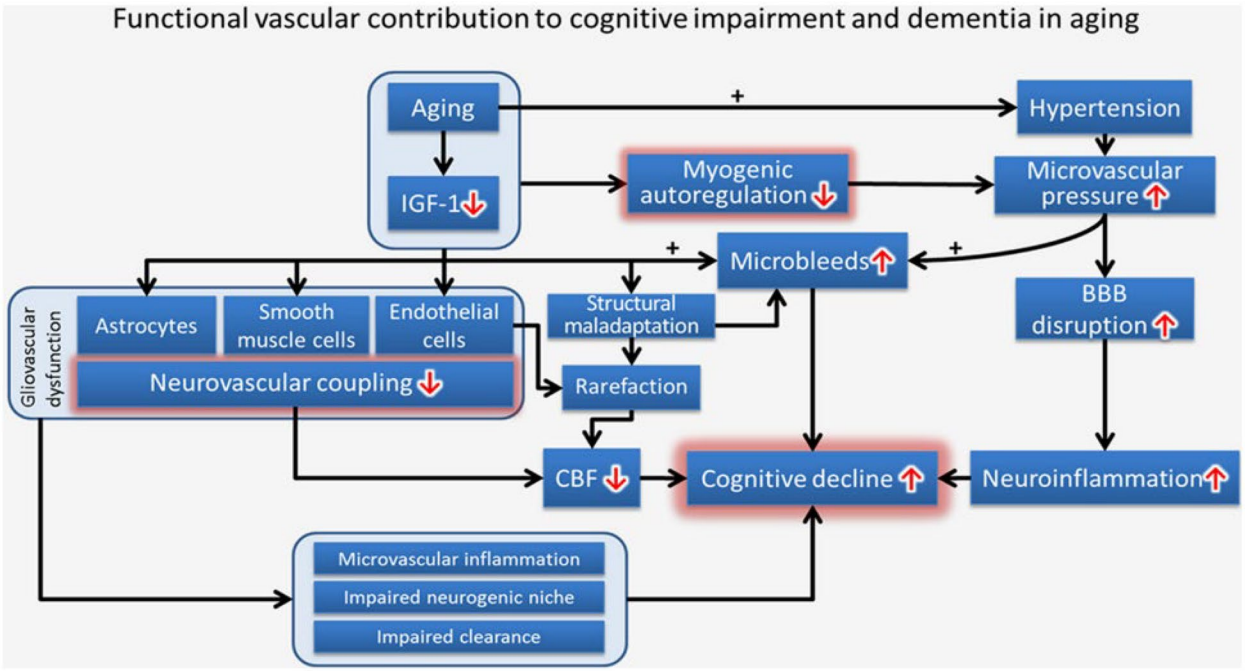

Fig. 6 Functional vascular contributions to cognitive impairment and dementia in aging. The schematic representation illustrates the interrelated microvascular mechanisms that contribute to age-related cognitive decline. The model highlights that age-related IGF-1 deficiency compromises the neurovascular unit, impairing the function of astrocytes, endothelial cells, and smooth muscle cells. The resulting endothelial dysfunction and decreased no bioavailability, increased oxidative stress, and/or dysregulation of astrocytic mediators contribute to neurovascular uncoupling, which impairs cognitive function due to inadequate supply of oxygen and nutrients to active brain regions. Age-related impairment of microvascular homeostasis, including alterations of myogenic autoregulatory mechanisms, renders the aged brain more susceptible to damage induced by comorbid conditions such as hypertension. In particular, the model predicts that impaired myogenic adaptation to hypertension promotes both the pathogenesis of cerebral microhemorrhages and blood–brain-barrier disruption, contributing to neuronal damage and cognitive decline. Aging and age-related IGF-1 deficiency also promote structural remodeling of the cerebral microcirculation, including microvascular rarefaction, contributing to an age-related decline in cerebral blood flow. They also promote structural maladaptation to hypertension, increasing microvascular fragility. Additionally, age-related microvascular proinflammatory alterations, impairment of vascular clearance of toxic waste products (such as Aβ) and metabolic by-products from the brain parenchyma and impaired trophic function of the microvascular endothelium that regulate stem cell self-renewal and differentiation in neurogenic niches could be implicated in impaired cognitive function. [54] Source: Toth et al (2017)

arterial stiffness on the rate of cognitive decline. In a cohort of 6.927 individuals with a mean age of 58.8 years, high carotid-femoral PWV was found to be associated with low performance in verbal fluency and memory tests, regardless of systolic BP [13].

Therefore, PWV analysis stands out as an essential tool in the early identification of cognitive alterations related to vascular aging and HT. Its clinical use makes it possible not only to monitor the progression of arterial stiffness but also to implement preventive strategies to minimize the impact of associated cardiovascular and neurological conditions, such as dementia and cognitive decline.

3.8 Vascular Aging and Decline Cognitive

The prevalence of dementia increases exponentially with advancing age, from 5% at the age of 65 to 20% at the age of 80 and 40% at the age of 90, which highlights the significant impact of this condition. Between 1990 and 2016, the global prevalence of the syndrome grew by 117%, making it the fifth leading cause of death worldwide. In 2019, it was estimated that 55 million people in the world were living with dementia [70, 71].

In Brazil, data from the ELSI-Brazil study indicated a prevalence of dementia of 5.8% among individuals aged 60 and over [71]. Population studies show that this prevalence increases progressively with age, ranging from 3.2% to 5.3% in the 60–64 age group and reaching up to 71.4% among individuals aged over 90.

Cognitive impairment, characterized by memory loss, learning difficulties, and reduced ability to concentrate, can range from mild deficits, often not clinically detectable, to dementia. The latter is defined as a syndrome characterized by cognitive decline, with or without behavioral changes, which interferes with activities of daily living (ADLs), provided it is not associated with psychiatric disorders or delirium [72]. The clinical spectrum includes subjective cognitive decline (SCD), which presents memory complaints without changes in neuropsychological tests; mild cognitive impairment (MCI), in which there is cognitive impairment without significant impairment of ADLs; and dementia, in which the decline interferes with the individual's independence [73–75].

Vascular aging plays a fundamental role in the genesis of cognitive deficits and the risk of dementia, due to a complex interaction of pathophysiological mechanisms [76]. The relationship between microcirculation and macrocirculation forms a vicious cycle in which damage to the small arteries increases peripheral resistance, raising mean arterial pressure and causing hardening of the large arteries. This process promotes higher central systolic pressure, perpetuating damage to target organs, and increasing the risk of cardiovascular and neurological complications [77].

Arterial stiffness has been consistently associated with mild cognitive impairment and dementia [78]. In the ARIC-NCS study of 3550 participants, elevated PWV was related to a higher prevalence of dementia, while elevated cPP showed an association with both dementia and MCI [4]. Macrostructural and microstructural brain damage, as well as diseases of the small cerebral vessels, are often identified before the onset of dementia-related diseases such as Alzheimer's and other types of cognitive decline. This condition is also related to a reduction in gray matter volume and indicators of microvascular diseases, such as white matter hyperintensities, microbleeds, and LI [69, 79].

Studies such as the "Nuns' Study" reinforce the role of cerebrovascular diseases in the clinical manifestation of Alzheimer's disease (AD). Elderly women with cerebral infarcts associated with AD showed worse cognitive function compared to those without infarcts [80].

Notably, evidence suggests that up to 40% of dementia cases could be prevented by addressing modifiable risk factors, with HT being the main cardiovascular factor. It is argued that up to half of Alzheimer's patients have cerebrovascular lesions [81, 82]. AH in middle age is associated with changes in memory, executive function, and global cognition, due to increased pulsatile stress and vascular remodeling [83–85].

A systematic review and meta-analysis highlighted that white matter hyperintensities (WMH), LI, and cerebral microhemorrhages (CMB) are widely prevalent markers in the population and are strongly associated with a significant increase in the risk of stroke, dementia, and mortality. A high burden of WMH, LI, and CMB was related to a twofold increased risk of ischemic stroke and a threefold increased risk of hemorrhagic stroke. In addition, the significant presence of WMH was associated with an increased risk of dementia and Alzheimer's disease, with risk ratios ranging from 1.5 to 1.8. Likewise, high loads of these markers were correlated with an increase in mortality, with risk ratios between 1.5 and 2.0 [86].

Recent research indicates a significant relationship between vascular risk factors and biomarkers such as beta-amyloid protein (Aβ) and phosphorylated tau (p-tau), both pathological elements of AD. These biomarkers precede alterations such as brain atrophy and the development of cognitive impairment [87]. Evidence shows that arterial stiffness is associated with the extent and progression of Aβ plaques in the brain, as assessed by positron emission tomography in older adults without signs of dementia [88]. These associations have been

confirmed in studies with diverse populations, showing consistency in both white and black older adults [89].

These findings highlight the importance of arteriosclerosis over atherosclerosis as the main therapeutic target for preventing cerebrovascular disease and cognitive decline, to preserve the structural and functional integrity of the brain. The robustness of the evidence linking arterial stiffness to dementia highlights the need for further research, such as clinical trials, to explore the links between the progression of arterial stiffness and the onset of dementia. This reinforces the central role of arterial stiffness in understanding the mechanisms that lead to cognitive decline.

3.9 Intracranial Pressure

Cerebral vascular aging has been evaluated as a relevant factor in cognitive decline and the development of dementia. Despite the relevance of this relationship for understanding these diseases, there is still no specific biomarker to quantify cerebral vascular aging. This gap is remarkable, considering that vascular aging is not restricted to structural changes in the vessels, but also affects important functions such as CBF and vascular stiffness, with a direct impact on ICP.

ICP can be elevated due to impaired cerebral autoregulation resulting from vascular aging. Arterial stiffness, often observed with advancing age, reduces the ability of vessels to adapt to pressure variations, compromising cerebral autoregulation and constant CBF [64]. This loss of vascular elasticity makes the brain more susceptible to pressure variations, increasing ICP and, consequently, the risk of permanent brain damage, such as cerebral edema and ischemia [88, 90, 91].

In addition, vascular aging can contribute to increased ICP through changes in cerebral microcirculation, such as small vessel disease, which can cause lacunar infarcts and cerebral microhemorrhages [92]. Impairment of the blood–brain barrier (BBB) can also exacerbate the formation of cerebral edema [93]. These cumulative effects promote an increase in ICP and can lead to the development of intracranial hypertension (ICH).

The consequences of ICH on the brain can be severe, including CBF restriction, which can result in permanent neurological damage, such as cognitive and vascular dementia [94]. Other complications include cerebral edema, cerebral herniation, papilledema, ischemia, and symptoms such as severe headaches [95]. Thus, monitoring ICP is relevant, especially in individuals with AVA, since this process compromises both the structure and functionality of cerebral vessels, increasing the risk of serious complications.

Traditional ICP monitoring is carried out invasively in intensive care settings, using intracranial devices which, although accurate, carry significant risks such

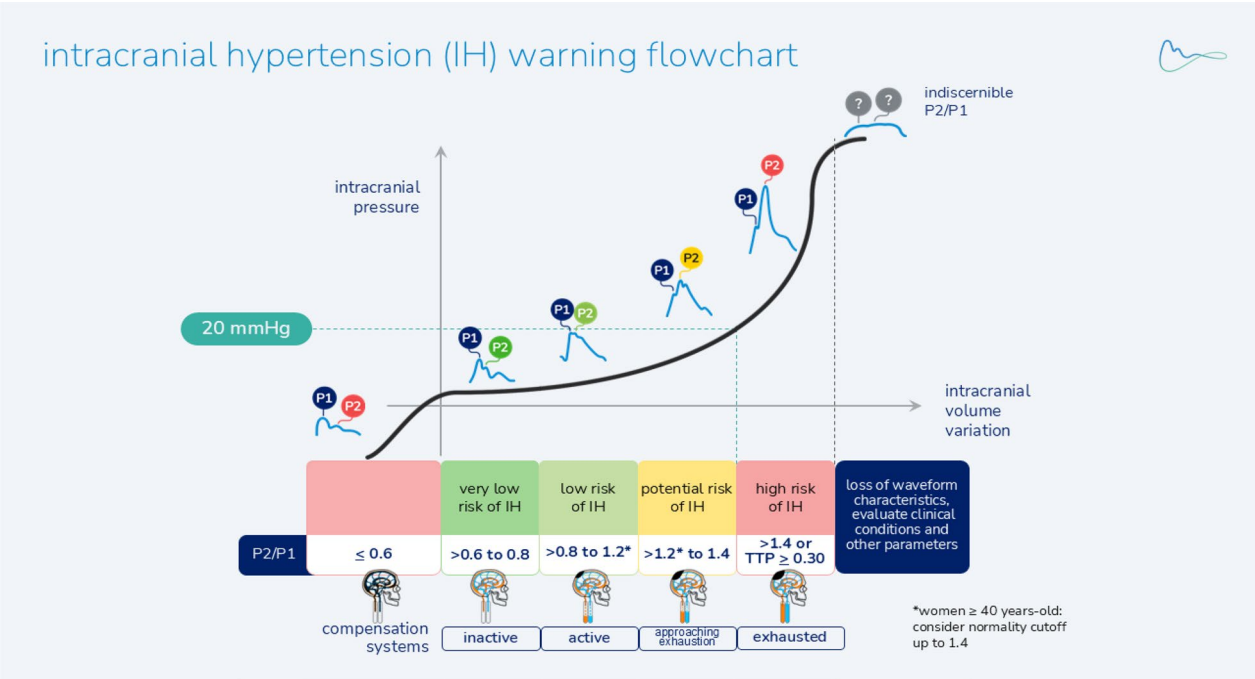

Fig. 7 Intracranial hypertension alert flow. P1 peak corresponds to the systolic component of blood pressure, P2 reflects cerebral compliance, and P3 is related to venous blood flow. *TTP* time to peak, *HIC* intracranial hypertension. [94] Source: Based on Ocatomo et al. (2024)

as infection and bleeding. Non-invasive methods, such as ultrasound of the optic nerve, allow for the pinpoint detection of ICH that has already occurred. However, the brain4care system has emerged as an innovative alternative, capable of monitoring ICP continuously and non-invasively by analyzing micrometric cranial expansions. This method provides detailed data on the morphology of the pressure wave, such as the P2/P1 ratio and peak time, as shown in Fig. 7 [96–98].

The ICP wave is made up of three peaks (P1, P2, and P3), which represent different aspects of cerebral hemodynamics. The P1 peak corresponds to the systolic component of BP, P2 reflects cerebral compliance, and P3 is related to venous blood flow. Under normal conditions, the relationship between the peaks is P1>P2>P3 but this relationship changes when cerebral compliance is compromised or ICP rises [99]. Wave morphology analysis could be a promising tool for investigating cerebral vascular aging, integrating intracranial data to develop new diagnostic approaches.

Although there are still no studies that directly relate the behavior of the ICP wave to cerebral vascular aging, evidence suggests that arterial stiffness, measured by PWV, is associated with changes in CBF, which may contribute to increased ICP. A recent study by Liu et al. (2021) showed that arterial stiffness is negatively correlated with CBF in hypertensive men, using magnetic resonance imaging and specialized tools to assess intracranial vascular function [100]. Similar results were observed by Jefferson et al. (2018) and Tarumi et al. (2011), who identified an inverse relationship between carotid-femoral PWV and CBF in patients with no history of cerebrovascular events [101, 102]. Additionally, studies have recently been published showing that increased blood pressure can lead to increased ICP [103–105].

In addition, several studies have highlighted the relationship between chronological aging and increased cerebral arterial stiffness [66, 106–109]. Fico et al (2022) analyzed the impact of age on the cerebral pulsatility index, an important indicator of intracranial compliance in clinical practice [107]. The findings indicated that both age and carotid-femoral PWV are significant predictors of ICP, suggesting that increased ICP may be associated with arterial stiffness and small vessel disease.

Therefore, vascular aging, characterized by arterial stiffness and increased PWV, is directly associated with cognitive decline due to its effects on the cerebral vasculature and neurovascular unit. This results in greater transmission of pulsatile energy to the small vessels of the cerebral microcirculation, causing structural and functional damage such as edema and increased intracranial volume. In addition to this effect, arterial stiffness also compromises cerebral autoregulation, making it difficult to maintain constant blood flow in the face of variations in systemic BP, which can lead to a significant increase in ICP due to small volumetric variations. Thus, PWV is indirectly associated with ICP, and the behavior of the ICP wave could be explored as a potential biomarker to show changes in cerebral compliance.

4 Conclusion

Vascular aging is associated with structural and functional changes in the vasculature, such as increased arterial stiffness and reduced adaptive capacity of blood vessels. These changes can compromise cerebral perfusion and vascular autoregulation, favoring the progression of cognitive dysfunction over time. Arterial stiffness, often assessed by pulse wave velocity, has been linked to changes in cerebral blood flow and can impact both autoregulation and intracranial compliance, which reinforces its possible link with cognitive decline. In this context, the behavior of intracranial pressure could be considered a potential biomarker for monitoring cerebral vascular aging, allowing for a more accurate assessment of brain dynamics. Further studies are needed to deepen this relationship and explore its potential in the early identification of cognitive impairment and in the development of diagnostic and therapeutic strategies to minimize the impacts of vascular aging on the brain.

Abbreviations

BP	Blood pressure
CVD	Cardiovascular disease
AVA	Accelerated vascular aging
EVA	Early vascular aging
HT	Hypertension
cPAS	Central systolic blood pressure
cPP	Central pulse pressure
Aix	Augmentation Index
PWV	Pulse wave velocity
cPAD	Central diastolic blood pressure
LV	Left ventricle
ADL	activities of daily living
MCI	mild cognitive impairment
ADRD	Other types of cognitive decline
AD	Alzheimer disease
WMH	white matter hyperintensities
LI	lacunar infarcts
CBF	Cerebral blood flow
ICP	Intracranial pressure
BBB	Blood–brain barrier
ICH	Intracranial hypertension

Acknowledgements

We gratefully acknowledge the support of the funding agencies: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

Author Contributions

MCC, ARB, ARCC, and ROO wrote and participated in the design of the article. MHJL wrote the article. SI, ACO, MTAP, PVTP, and GF revised the article. WKSB designed, conceived, and revised the article.

Funding
Not applicable.

Availability of Data and Materials
No datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest
GF declares that he is co-founder and scientific director of brain4care. The other authors declare that they have no conflict of interest.

Ethics Approval and Consent to Participate
Not applicable

Consent for Publication
Not applicable

Competing interests
GF declares that he is co-founder and scientific director of brain4care. The other authors declare that they have no conflict of interest.

Received: 28 March 2025 Accepted: 24 May 2025
Published online: 13 June 2025

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