



HHS Public Access

Author manuscript

Hypertension. Author manuscript; available in PMC 2025 January 01.

Published in final edited form as:

Hypertension. 2024 January ; 81(1): 34–44. doi:10.1161/HYPERTENSIONAHA.123.19939.

Basic Mechanisms of Brain Injury and Cognitive Decline in Hypertension

Caroline E. Baggeroer¹, Francis E. Cambroner¹, N. Anna Savan², Angela L. Jefferson^{1,3,4},
Monica M. Santisteban^{1,3,4}

¹Vanderbilt Memory and Alzheimer's Center, Vanderbilt University Medical Center, Nashville, TN

²Medical Scientist Training Program, Yale University, New Haven, CT

³Department of Neurology, Vanderbilt University Medical Center, Nashville, TN

⁴Department of Medicine, Vanderbilt University Medical Center, Nashville, TN

Abstract

Dementia affects almost 50 million adults worldwide, and a major cause of death and disability. Hypertension is a leading risk factor for dementia, both Alzheimer disease and Alzheimer disease related dementias. Although this association is well-established, the mechanisms underlying hypertension-induced cognitive decline remain poorly understood. By exploring the mechanisms mediating the detrimental effects of hypertension on the brain, studies have aimed to provide therapeutic insights and strategies on how to protect the brain from the effects of blood pressure elevation. In this review, we focus on the mechanisms contributing to the cerebrovascular adaptations to elevated blood pressure and hypertension-induced microvascular injury. We also assess the cellular mechanisms of neurovascular unit dysfunction, focusing on the premise that cognitive impairment ensues when the dynamic metabolic demands of neurons are not met due to neurovascular uncoupling, and summarize cognitive deficits across various rodent models of hypertension as a resource for investigators. Despite significant advances in antihypertensive therapy, hypertension remains a critical risk factor for cognitive decline, and several questions remain about the development and progression of hypertension induced cognitive impairment.

Keywords

Cerebral small vessel disease; hypertension; cognitive decline; dementia; Alzheimer's disease; neurovascular unit

INTRODUCTION

Understanding the mechanistic relationship between cognitive decline and vascular health is essential, especially as human life expectancy increases and dementia remains a leading cause of death and disability¹. Nearly half the adults in the United States are

Correspondence Monica M. Santisteban, PhD, monica.santisteban@vmc.org, 2213 Garland Ave, 1235 Light Hall, Nashville, TN 37232.

The authors declare no conflicts.

diagnosed with hypertension², making it one of the most prevalent vascular risk factors for cognitive impairment and dementia. The association between hypertension and risk of dementia is well established³, yet the mechanisms underlying this association remain under investigation. Studies to date suggest that hypertension not only induces cerebrovascular adaptations that are detrimental to the brain, but it also has a direct impact on the cerebral vasculature and neurovascular unit⁴. Understanding both the molecular and cellular mechanisms underlying this damage is essential to identify novel therapeutic targets and interventions, and ultimately prevent permanent brain damage and cognitive decline.

This review highlights the impact of hypertension on the neurovasculome⁵, the entire extracranial and intracranial vasculature and associated cells pertaining to the skull, brain, and meninges, focusing on potential mechanisms of neuronal injury and cognitive decline. A mechanistic discussion of the cerebrovascular adaptations, in both the extracranial and intracranial vasculature, and microvascular injury in response to elevated blood pressure is presented to understand how hypertension alters the brain vasculature. Then, the neurovascular unit (NVU) is examined in detail to explore the effects of hypertension on each specific cell type. Although important and highly relevant, the intersection between hypertension and classical Alzheimer's disease pathology (amyloid deposition and tau tangles) has been previously discussed^{4,6}, and is thus not included in the present review. Finally, we provide a summary of cognitive deficits in selected rodent models of hypertension and potential associated mechanisms as a tool for future investigation.

CEREBROVASCULAR ADAPTATIONS IN LARGE ARTERIES AND ARTERIOLES

The brain is a major target of end-organ damage in hypertension, and alterations affecting the cerebral vasculature may lead to vascular insufficiency and neuronal dysfunction³. Chronic elevations of blood pressure increase pulsatile stress on the cerebral vasculature, and as a result they will undergo significant adaptation to protect downstream microvessels and maintain adequate cerebral blood flow (CBF) regulation⁷. The cerebral vasculature will undergo inward remodeling, a rearrangement of the vascular smooth muscle cells (VSMC) that reduces lumen diameter, and vascular hypertrophy, an increase in vascular wall thickness resulting from VSMC proliferation and increased cell volume⁸. Several studies support a role for angiotensin II (AngII) signaling, a hormone involved in hypertension, as an important contributing mechanism to cerebrovascular remodeling and hypertrophy⁹. Although oxidative stress alone is not sufficient to induce remodeling¹⁰, NADPH oxidase 2 (Nox2)-derived radicals induced by AngII type 1 receptor (AT1R) activation are an important contributing mechanism to cerebrovascular remodeling¹¹. However, other factors may also be important, including altered VSMC mechanotransduction mechanisms¹², mineralocorticoid signaling¹³ or calcium-activated chloride channel function¹⁴.

Hypertension is also a common co-morbidity with the reduced distensibility, and compliance of vasculature known as arterial stiffening¹⁵. Although this process can occur throughout the body, it is particularly detrimental in the aorta and carotid arteries which are essential to delivery of oxygen and nutrients to the brain¹⁵. Elevated arterial pressure causes mechanical

stress on the vasculature, resulting in the elastin fragmentation, collagen deposition, and subsequent increase in vascular stiffness⁹. Thus, arterial stiffening hinders the process of healthy continuous blood flow by exposing the smaller, less compliant cerebral capillaries to high velocity pulse waves of blood¹⁶. Dynamic cytoskeletal and cell-matrix interactions which regulate VSMC function and elasticity may also play a role in arterial stiffening, and interestingly these alterations are suggested to be AT1R-dependent¹⁷. Importantly, human studies have associated aortic stiffening and resulting increased pulse wave velocity with cognitive impairment and neurodegenerative biomarkers¹⁸. Research on the mechanisms behind these associations is limited, but animal studies suggest that the reduced compliance of large arteries reduce resting CBF¹⁶, disrupt the blood-brain barrier (BBB)¹⁶, and induce marked cerebral gliosis mediated by oxidative stress¹⁹. However, the molecular mechanisms of neuronal dysfunction remain to be uncovered.

Lastly, hypertension is also associated with atherosclerosis, and particularly atherosclerosis in the Circle of Willis, which results in cerebral hypoperfusion and may be an indirect way hypertension contributes to AD²⁰. Of note, these adaptations in large arteries and arterioles have significant effects on the downstream vasculature and thus make relevant contributions to cognitive decline.

MICROVASCULAR INJURY

Cerebral small vessel disease (CSVD) is a multifaceted vascular disease that impacts arterioles, capillaries, and small veins supplying deep structures and white matter of the brain, and represents the most prevalent vascular risk factor for dementia²¹. CSVD is typically characterized in brain MRIs by white matter lesions, lacunar infarcts, enlarged perivascular spaces, and cerebral microbleeds (Fig. 1)²¹. White matter lesions are densities identified on FLAIR MRIs that are characterized by decreased vascular density, vessel wall thickening, increased vessel tortuosity, and plasma proteins²¹. These lesions typically result in demyelination of neurons, gliosis, and loss of fibers and oligodendrocytes²¹. There are several hypotheses on the etiology of white matter lesions, including flow-dependent mechanisms such as ischemia, vasculopathy, reduced white matter perfusion, and flow-independent mechanisms such as loss of pericyte coverage and BBB breakdown^{21,22}, inflammation, and activation of endothelial cells within capillaries²¹. Hypertension, which is an important risk factor for white matter lesions²¹, causes increases in blood vessel fibrosis and altering of the structural integrity of arterioles and capillaries⁹. Lacunes are also an MRI-defined feature of CSVD highly associated with hypertension and are characterized as small deep brain infarcts caused by occlusions of branches of large cerebral arteries, including the middle cerebral artery and the Circle of Willis²³. These infarcts typically appear in the deep white matter and contain necrotic waste and have evidence of gliosis, myelin loss, and neuronal loss²³. Enlarged perivascular spaces are also a neuroimaging marker of CSVD. Perivascular spaces are cerebrospinal fluid (CSF) filled spaces surrounding the penetrating arterioles and are important for drainage of interstitial fluids²⁴. While the primary cause of enlarged perivascular spaces is not known, both animal and human studies suggest inflammation may play an important role²⁴.

Hypertension is also a major risk factor for cerebral microbleeds^{25,26}. Although the mechanisms leading to cerebral microbleeds are still under investigation, their pathogenesis is thought to be initiated by oxidative stress and inflammation weakening the structural integrity of the microvessels and thus allowing them to rupture²⁵. Furthermore, hypertension-induced microbleeds are also worsened by aging²⁷ and amyloid pathology²⁸. Cerebral microbleeds are associated with worse cognitive function and the mechanisms may involve local brain injury and long-lasting inflammation²⁹.

Microvascular rarefaction refers to the reduction of arteriolar and capillary density. Functional rarefaction refers to reversible constriction and reduction of capillaries, while structural rarefaction is an irreversible loss of arterioles and capillaries³⁰. It is hypothesized that long-term, functional rarefaction precedes the permanent structural changes³⁰. Indeed, arteriolar and capillary rarefaction is observed in many animal models of hypertension³¹ and in hypertensive patients, specifically at the earlier stages³². The mechanisms underlying cerebral microvascular rarefaction in hypertension are complex and remain under investigation but have been suggested to be a consequence of the transmission of increased pressure to the brain microvessels⁶, and particularly pre-capillary arterioles and post-capillary venules are sensitive to the increased resistance in hypertension. Endothelial cell dysfunction may directly contribute to rarefaction of cerebral vessels⁶, but also indirectly by reducing cross-talk between endothelial cells and pericytes thus inducing loss of pericytes and ultimately reduction in capillary density³³. This may lead to the formation of string vessels, or collapsed remnants of basement membrane that have no endothelial cells³⁴. Interestingly, venular rarefaction has been reported in the retinal vasculature during malignant hypertension³⁵. Additional supporting evidence of the multifactorial pathogenesis come from studies indicating that hypertension-induced cerebral microvessel rarefaction is exacerbated by aging³¹, but may be rescued by exercise³⁶ and reducing lipid levels³⁷. Of note, the CRUCIAL study (evaluation of microvascular rarefaction in vascular cognitive impairment and heart failure) is expected to report first results in 2025 and is planning to develop novel non-invasive measures for detection of cerebral microvascular rarefaction³⁸, which will contribute to furthering our understanding of hypertension-induced microvascular rarefaction and its contribution to cognitive impairment.

NEUROVASCULAR UNIT DYSFUNCTION

The brain has a high and dynamic metabolic demand that requires tight regulation of CBF throughout the system. Brain, vascular, and perivascular cells work together as a unit to maintain the homeostatic environment of the brain. Neurovascular coupling is known as the ability of the cerebral vasculature to increase local CBF to regions with enhanced neuronal activity and is essential to the maintenance of proper neuronal function³⁹. Importantly, the bidirectional communication between the vasculature and neurons is an important physiological mechanism that may be impaired in dementia. The complex nature of the NVU in health has been previously reviewed³⁹, thus in this section we will focus on the hypertension-induced effects on the NVU (Fig. 2) and their potential association with cognitive impairment. This is based on the hypothesis that cognitive impairment occurs when the metabolic demands of neurons are not met due to neurovascular uncoupling^{40,41}. Neurovascular uncoupling in hypertension most commonly presents as a reduction or

absence of vasodilation in response to neuronal activity, although in acute brain injury can also present as vasoconstriction leading to a reduction in local CBF in response to neural activity (inverse neurovascular coupling)⁴². Interestingly, a recent study described a prolonged inverse hemodynamic response in stroke-prone salt-sensitive spontaneously hypertensive rats⁴³. In this review, we will discuss all cells involved with cerebral arterioles, capillaries, and venules as members of the NVU.

Endothelial cells

Endothelial cells participate in CBF regulation by modulating vasomotor tone through the release of vasoactive signals, including both constrictor and relaxing factors⁴⁴. Hypertension has profound effects on endothelial-mediated vasodilation⁸, particularly associated with reduced nitric oxide (NO) bioavailability⁷. Experimental studies have found that endothelial NO synthase (eNOS) function is impaired in various models of hypertension, ranging from reduced expression, mislocalization, modulation of activating and inhibitory phosphorylation sites, and eNOS uncoupling; thus resulting in reduced NO production⁴⁵. Furthermore, superoxide may scavenge NO, thus vascular oxidative stress further limits NO bioavailability^{8,44}. Finally, although studies have suggested a link between endothelial dysfunction and cognitive impairment⁴⁶, the question remains whether this association is mediated by a direct effect of CBF or via correlation with CSVD severity⁴⁷.

Endothelial cells are also important in sensing and transmitting neurovascular signals during neurovascular coupling³⁹. Neural activity is postulated to activate endothelial $K_{IR}2.1$ channels, resulting in endothelial cell hyperpolarization, and retrograde propagation of vasodilation⁴⁸. Increased aldosterone, induced by long-term treatment with an angiotensin receptor blocker (ARB), may damage $K_{IR}2.1$ signaling in hypertension, resulting in impaired capillary-to-arteriolar signaling⁴⁹ contributing to neurovascular uncoupling. However, ARB use is not detrimental to cognitive function, therefore this mechanism may not be widespread in hypertensive cognitive decline. On the other hand, the recent description of a prevalent continuum of renin-independent aldosterone production that parallels hypertension severity in essential hypertensive patients raises the possibility that this mechanism may be more relevant than previously recognized. Given the regional heterogeneity observed in brain endothelial cells both at the level of vascular segments⁵⁰ and brain regions, future investigation should evaluate the effects of hypertension, and associated molecules (Ang II, aldosterone), on different vascular segments as well as across brain regions.

Endothelial cells also form the first layer of the BBB, a unique property of the brain vasculature regulating the bidirectional transport of molecules between the brain and the blood⁴⁵. BBB disruption in hypertension has been suggested to be mediated by AngII⁵¹ and reactive oxygen species⁵², rather than the increase in systolic pressure itself^{51,53}. AngII in the circulation activates cerebral endothelial AT1R leading to tight junction remodeling, increased vesicular transport, and BBB disruption⁵³. However, studies have also shown that venules are a key site of BBB disruption during inflammation and are particularly sensitive to increases in pressure in both acute and chronic hypertension^{54,55}. In humans, BBB breakdown is an early biomarker of cognitive impairment⁵⁶, specifically BBB breakdown

in the hippocampus worsened mild cognitive impairment⁵⁷. Although BBB disruption is present in some patients with hypertension⁵⁸, and may be associated with changes in daily blood pressure profile⁵⁹, it has not been widely reported as a key feature of hypertension. Whether this is a result of the difficulty to evaluate the effect of hypertension in the presence of other comorbidities, or a true indication of the low prevalence of BBB disruption in the human patient population remains to be determined.

Mural cells

Smooth muscle cells are present in cerebral arteries and arterioles, and are important for the maintenance of cerebral autoregulation - the ability of the cerebral circulation to maintain CBF relatively constant over a range of arterial pressures⁴⁴. Importantly, autoregulation is affected by the rate at which blood pressure fluctuates⁶⁰, such that relatively slow changes in arterial blood pressure are associated with stable CBF, while rapid changes result in greater variability in CBF. Static autoregulation refers to the classic steady-state relationship between arterial blood pressure and CBF, while dynamic autoregulation refers to a CBF response occurring over seconds to minutes due to fast changes in blood pressure⁶⁰. Static autoregulation is impaired in various animal models of hypertension⁶⁰ potentially via increased myogenic tone⁴⁴ as well as structural adaptations to the elevated blood pressure. These findings suggested that hypertension increases the risk for hypoxia if blood pressure were to drop below the lower limit of autoregulation and thus could be a contributing mechanism to neuronal injury. Although cerebral autoregulation was also thought to be impaired in human hypertension, increasing evidence indicates that static autoregulation is actually maintained in hypertensive patients⁶⁰. On the other hand, whether hypertension affects dynamic cerebral autoregulation is still under debate⁶⁰, as some studies suggest it is maintained, while others report impairments. It may be important to investigate the functional heterogeneity of dynamic autoregulation across brain regions to better understand the potential effects on cognitive function.

Pericytes are mural cells present in the microvasculature (pre-capillary arterioles, capillaries, and post-capillary venules) involved in regulating blood flow⁶¹ as well as maintenance of the BBB⁶². Pericytes vary in their location, morphology, protein expression, and related functions, many of which are still being identified. Morphologically, they are surrounded by basement membrane and extend processes both along and around capillaries, with more circumferential processes at the arteriole end of the capillary bed, more longitudinal processes in the middle of the capillary bed, and a stellate morphology at the venule end of the capillaries⁶³. These morphological differences have led to “zone-specific” nomenclature: on precapillary arterioles (e.g., ensheathing pericytes, transitional pericytes), on capillaries (e.g., thin-strand or helical pericytes), and on post-capillary venules (e.g., mesh pericytes). Notably, there is variation in pericyte gene expression too, wherein downstream mural cells from capillary to venule zones are characterized by high expression of membrane transporters, such as *abcc9* (ATP binding cassette subfamily C member 9) and pericytes that give out more circumferential processes expressing more alpha-smooth muscle actin (α -SMA)⁶⁴. Pericyte loss has been associated with impairment of neurovascular coupling, BBB disruption, and cognitive impairment. Pericytes may also be playing an important mechanistic role in the breakdown of the BBB³¹, white matter lesions²², and development

of cognitive impairment. Early studies have reported both increased and decreased brain pericyte numbers in hypertensive rodent models^{65,66}. However, limitations in the methods of pericyte identification used prevented definitive conclusions from being drawn. More recent studies have found a loss of pericyte coverage of capillaries in hypertension, which is further exacerbated by aging³¹, and can be prevented by interferon-gamma blockade⁶⁷. AngII can directly stimulate pericyte migration and contraction⁶⁸ and may also upregulate Nox4 expression⁶⁹. While Nox4 has been considered protective in endothelial cells⁷⁰, pericyte Nox4 is associated with promoting blood-brain barrier damage through activation of NF-Kb and matrix metalloproteases⁷¹ and mediating vasoconstriction of capillaries⁷². Thus, Ang II-induced Nox4 upregulation in pericytes may contribute to the neurovascular unit dysfunction observed in hypertension. RNA-sequencing of cerebral microvascular pericytes from normotensive and hypertensive rats identified several differentially expressed genes and signaling pathways related to cell adhesion, extracellular matrix interactions, and inflammation⁷³, consistent with their possible role in BBB disruption. However, whether disruption of pericyte function in hypertension contributes to cognitive impairment has not been determined.

Astrocytes

Astrocytes are important members of the NVU contributing to both BBB integrity and neurovascular coupling. Swelling of astrocytic endfeet can be observed around capillaries in hypertensive rats and may be an indication of BBB disruption⁶⁶. With regards to neurovascular coupling, astrocytes may respond to neuronal activity by releasing vasoactive mediators⁷⁴, and two recent studies reported that AngII augments astrocytic calcium signaling^{75,76}. These findings raise the possibility that astrocytes contribute to the increased vascular tone and disruption of neurovascular coupling in hypertension. However, the importance of altered astrocytic calcium signaling or astrocytic endfeet swelling on cognitive function in hypertension remains to be determined.

Microglia

While microglia are commonly known in neurodegeneration for their role in neuroinflammatory processes, and particularly contributing to Alzheimer's disease pathology⁷⁷, they have recently been implicated in cerebrovascular function⁷⁸. A subpopulation of microglia, known as juxtavascular or capillary-associated microglia⁷⁸, are located in close proximity of brain microvessels, specifically in direct contact with the capillary basement membrane without disrupting astrocytic endfeet or pericyte coverage of microvessels. Microglia depletion with the CSF1 receptor inhibitor PLX3397 triggered capillary diameter dilation by approximately 15%, an increase in blood flow of about 20% assessed by laser-speckle, and impaired vasodilation to hypercapnia⁷⁸. However, it's important to note that PLX3397 targets all microglia, not only the capillary-associated subpopulation, while CSF1 receptor inhibition also depletes about 60% of brain macrophages⁷⁹. Thus, it is not possible at this time to rule out the contribution of parenchymal microglia or brain macrophages to mediating the observed effects. Nonetheless, given their implication in neuroinflammation and neurovascular regulation, determining their contribution to neurovascular dysfunction and cognitive impairment in hypertension should be a focus of investigation in coming years.

Perivascular macrophages

Found in the perivascular space surrounding cerebral arterioles and venules, perivascular macrophages (PVM) are innate resident immune cells that have emerged as new players of the NVU and are increased in aging and hypertension⁸⁰. PVM are one of three types of brain resident macrophages, and together with leptomeningeal and choroid plexus macrophages, they are known by various nomenclatures including central nervous system-associated macrophages, brain- or border-associated macrophages, or parenchymal border macrophages. However, given their localization to perivascular spaces, PVM are uniquely positioned to influence the cerebral vasculature. In rodent models of hypertension, PVM mediate the neurovascular dysfunction and disruption of the BBB via AT1R activation and Nox2-derived radicals^{53,81}. Given the sensitivity of the venular BBB⁵⁴, the presence of PVM-derived radicals may be particularly detrimental in this vascular segment. Depletion of PVM protects hypertensive mice from developing cognitive impairment^{53,79,81}, suggesting that PVM not only have a detrimental role in regulating cerebrovascular function in hypertension, but may also be key mediators in hypertensive cognitive decline. A recent report identified a new role of these cells in regulating CSF flow dynamics⁸², raising the possibility that dysfunctional PVM^{53,79,81} may be associated with impaired CSF flow in hypertension^{83,84}. This warrants future investigation on whether CSF flow and clearance mechanisms are affected in hypertension and may contribute to cognitive decline.

COGNITIVE DEFICITS IN RODENT MODELS OF HYPERTENSION

Given that no animal model can fully recapitulate the complex etiology of human hypertension⁸⁵, utilizing various models is necessary for thorough investigation of the mechanisms underlying hypertension-induced cognitive impairment. Supplementary Table S1 presents potential mechanisms of cognitive deficits in selected rodent models of hypertension as a resource for future investigation. It is important to note that large animal models, such as Rhesus monkeys⁸⁶, have also demonstrated hypertension-associated memory decline.

Genetic models of hypertension have a progressive rise in blood pressure with age, and thus are beneficial to investigate the effects of chronic spontaneous hypertension. Various genetic models develop cognitive deficits, including the spontaneously hypertensive rat (SHR), Schlager/blood pressure high (BPH/2) mouse, and human renin and angiotensinogen transgenic mice (R⁺/A⁺). Both the SHR and BPH/2 models develop such deficits at 12 weeks of age^{53,81,87}, and the R⁺/A⁺ transgenic mice at 16 weeks of age⁸⁸. In the BPH/2 mouse, impairments in spatial learning and memory^{81,89}, working memory^{53,81}, and disinhibition^{53,89} have been observed. However, it is important to note that we cannot rule out that the phenotypic effects observed are due to genetic differences unrelated to the elevation of blood pressure.

One of the most widely used models of hypertension, long-term subcutaneous infusion of AngII, varies widely in both dose and length of treatment⁸⁵. In rats, 2 months of AngII hypertension did not affect spatial learning and memory, but did impair cognitive flexibility assessed by a complex task⁹⁰. In mice, high doses of AngII administration for longer than 4 weeks is needed to induce cognitive deficits⁹¹. However, these high doses

may also induce anxiety⁹², and thus could make data interpretation more difficult. Despite extensive cerebrovascular structural and functional alterations induced in the AngII model of hypertension, and given that less than 15% of patients have elevated circulating renin-angiotensin system (RAS) activity, AngII-induced hypertension may not be the best suited model for assessing the effects of hypertension on cognitive function.

Salt-sensitivity affects up to 50% of patients with hypertension and has been identified as an independent risk factor for cardiovascular events⁹³. Rodent studies commonly use 4 or 8% NaCl, representing an 8-fold to 16-fold increase from a normal mouse diet⁹⁴. Although extremely high, these diets are comparable to the high end of the spectrum of human salt consumption⁹⁵. These high doses have been used historically because many rodent strains are resistant to salt treatment⁸⁵. A historical perspective and extensive list of salt-sensitive rodent models has been previously published⁹³, and thus will not be reiterated here. Both Dahl salt-sensitive⁹⁶ and DOCA-salt rats⁹⁷ have been reported to develop cognitive deficits in various domains, although the results are not always consistent. Given the independent link between salt and cognitive impairment in animals⁹⁴ and humans⁹⁸, further investigation on models of salt-sensitive hypertension is warranted.

Lastly, cognitive impairment has also been reported in surgical models of hypertension including transverse aortic coarctation (TAC)⁹⁹ and renovascular hypertension¹⁰⁰. TAC may be a particularly useful model because it presents with alterations to cerebrovascular reactivity, endothelial dysfunction, as well as neurodegenerative pathology, brain amyloid accumulation and BBB dysfunction⁹⁹.

CONCLUSIONS

While the relationship between hypertension and cognitive decline is undeniable, the mechanisms underlying this link are less well understood. Importantly, there are several big questions which remain in the field. First, how does impaired CBF regulation lead to cognitive impairment? As mentioned earlier, much of the studies investigating cerebrovascular mechanisms of cognitive impairment work under the assumption that cognitive impairment occurs when the metabolic demands of neurons are not met due to neurovascular uncoupling^{40,41}. However, the exact mechanisms linking impaired CBF to neuronal dysfunction and cognitive impairment are not clear. There are several hypotheses to explain this association: (1) the lack of oxygen availability resulting from reduced CBF could directly lead to neuronal death, (2) neuroinflammation in response to the leakage of plasma proteins in the brain parenchyma may be responsible for neuronal dysfunction, and (3) a neurotoxic milieu due to impaired clearance of byproducts of neuronal activity may impair neuronal function. Given that there is evidence for each of these in the literature, it is unlikely that only one of these hypotheses will explain the association. Instead, each of these mechanisms may be present to different degrees in individuals, and thus the combination of all three is important to cognitive health.

The second main question which remains is does restoring CBF in hypertension improve cognitive function? The answer may not lie exclusively in antihypertensive therapy. This is because even if the pharmacological lowering of blood pressure may improve CBF¹⁰¹, it

does not always rescue cognition¹⁰². Thus, even though hypertension treatment is essential and undoubtedly beneficial to cardiovascular health, it is important to recognize that there may be other processes operating in parallel that may contribute to cognitive decline in hypertension. This is complicated by the slow temporal progression of pathology, as the onset of hypertension and cognitive decline are separated by several decades⁷. Furthermore, aging exacerbates the detrimental effects of hypertension on the brain, and the interaction of aging and hypertension is a point of active investigation⁶. Therefore, protecting cognitive health will require early identification of patients at risk and prevention of CBF impairment.

Lastly, women are at much greater risk for dementia than men¹⁰³. This has historically been attributed to women living longer, though cardiovascular risk factors like hypertension may play a role in these differences. Women are more prone to hypertension after the age of 60¹⁰⁴, increasing the burden of elevated blood pressure and aging. This could be due to reduced estrogen signaling post-menopause as estrogen is important in nitric oxide signaling and a reduction in this could impact vasodilation¹⁰⁵. Estrogen is also important in the availability of elastin and collagen in the arterial walls, highlighting its importance in keeping compliant vessels walls¹⁰⁵. Additionally, estrogen is neuroprotective and plays a role in inflammatory regulation¹⁰⁶. Despite its essential roles, the effect of menopause on cardiovascular health and how that may contribute to dementia risk is understudied.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

SOURCES OF FUNDING

MMS was supported by grant number K22-NS123507 from the National Institutes of Health (NIH). FEC was supported by training grant T32-AG058524 (NIH). CEB, FEC, and ALJ were supported by grant number R01-AG034962 and K24-AG046373 from NIH. Figures were created on [Biorender.com](https://biorender.com).

REFERENCES

1. WHO. Global status report on the public health response to dementia. World Health Organization; 2021.
2. Bakris G, Sorrentino M. Redefining hypertension - assessing the new blood-pressure guidelines. *N Engl J Med*. 2018;378:497–499 [PubMed: 29341841]
3. Iadecola C, Yaffe K, Biller J, et al. Impact of hypertension on cognitive function: A scientific statement from the American Heart Association. *Hypertension*. 2016;68:e67–e94 [PubMed: 27977393]
4. Santisteban MM, Iadecola C, Carnevale D. Hypertension, neurovascular dysfunction, and cognitive impairment. *Hypertension*. 2023;80:22–34 [PubMed: 36129176]
5. Iadecola C, Smith EE, Anrather J, et al. The neurovasculome: Key roles in brain health and cognitive impairment: A scientific statement from the American Heart Association/American Stroke Association. *Stroke*. 2023;54:e251–e271 [PubMed: 37009740]
6. Ungvari Z, Toth P, Tarantini S, et al. Hypertension-induced cognitive impairment: From pathophysiology to public health. *Nat Rev Nephrol*. 2021;17:639–654 [PubMed: 34127835]
7. Iadecola C, Gottesman RF. Neurovascular and cognitive dysfunction in hypertension: Epidemiology, pathobiology and treatment. *Circ Res*. 2019;124:1025–1044 [PubMed: 30920929]
8. Pires PW, Dams Ramos CM, Matin N, Dorrance AM. The effects of hypertension on the cerebral circulation. *Am J Physiol Heart Circ Physiol*. 2013;304:H1598–1614 [PubMed: 23585139]

9. Humphrey JD. Mechanisms of vascular remodeling in hypertension. *Am J Hypertens.* 2021;34:432–441 [PubMed: 33245319]
10. Baumbach GL, Didion SP, Faraci FM. Hypertrophy of cerebral arterioles in mice deficient in expression of the gene for *cuZn* superoxide dismutase. *Stroke.* 2006;37:1850–1855 [PubMed: 16763183]
11. Chan SL, Baumbach GL. Deficiency of *nox2* prevents angiotensin ii-induced inward remodeling in cerebral arterioles. *Front Physiol.* 2013;4:133 [PubMed: 23805104]
12. Davis MJ, Earley S, Li YS, Chien S. Vascular mechanotransduction. *Physiol Rev.* 2023;103:1247–1421 [PubMed: 36603156]
13. Rigsby CS, Ergul A, Portik Dobos V, et al. Effects of spironolactone on cerebral vessel structure in rats with sustained hypertension. *Am J Hypertens.* 2011;24:708–715 [PubMed: 21350432]
14. Wang M, Yang H, Zheng LY, et al. Downregulation of *tmem16a* calcium-activated chloride channel contributes to cerebrovascular remodeling during hypertension by promoting basilar smooth muscle cell proliferation. *Circulation.* 2012;125:697–707 [PubMed: 22215857]
15. Safar ME, Asmar R, Benetos A, et al. Interaction between hypertension and arterial stiffness. *Hypertension.* 2018;72:796–805 [PubMed: 30354723]
16. Muhire G, Iulita MF, Vallerand D, et al. Arterial stiffness due to carotid calcification disrupts cerebral blood flow regulation and leads to cognitive deficits. *J Am Heart Assoc.* 2019;8:e011630 [PubMed: 31057061]
17. Fidelis HG, Mageski JGA, Goes SCE, et al. Blockade of angiotensin at(1) receptors prevents arterial remodelling and stiffening in iron-overloaded rats. *Br J Pharmacol.* 2020;177:1119–1130 [PubMed: 31705542]
18. Moore EE, Liu D, Li J, et al. Association of aortic stiffness with biomarkers of neuroinflammation, synaptic dysfunction, and neurodegeneration. *Neurology.* 2021;97:e329–e340 [PubMed: 34031194]
19. Sadekova N, Iulita MF, Vallerand D, et al. Arterial stiffness induced by carotid calcification leads to cerebral gliosis mediated by oxidative stress. *J Hypertens.* 2018;36:286–298 [PubMed: 28938336]
20. Eglit GML, Weigand AJ, Nation DA, et al. Hypertension and alzheimer’s disease: Indirect effects through circle of willis atherosclerosis. *Brain Commun.* 2020;2:fcaa114 [PubMed: 33543127]
21. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: Mechanisms and clinical implications. *Lancet Neurol.* 2019;18:684–696 [PubMed: 31097385]
22. Ding R, Hase Y, Ameen-Ali KE, et al. Loss of capillary pericytes and the blood-brain barrier in white matter in poststroke and vascular dementias and alzheimer’s disease. *Brain Pathol.* 2020;30:1087–1101 [PubMed: 32705757]
23. Nam KW, Kwon HM, Jeong HY, et al. Cerebral small vessel disease and stage 1 hypertension defined by the 2017 american college of cardiology/american heart association guidelines. *Hypertension.* 2019;73:1210–1216 [PubMed: 31067203]
24. Wardlaw JM, Benveniste H, Nedergaard M, et al. Perivascular spaces in the brain: Anatomy, physiology and pathology. *Nat Rev Neurol.* 2020;16:137–153 [PubMed: 32094487]
25. Ungvari Z, Tarantini S, Kirkpatrick AC, et al. Cerebral microhemorrhages: Mechanisms, consequences, and prevention. *Am J Physiol Heart Circ Physiol.* 2017;312:H1128–h1143 [PubMed: 28314762]
26. Petrea RE, O’Donnell A, Beiser AS, et al. Mid to late life hypertension trends and cerebral small vessel disease in the framingham heart study. *Hypertension.* 2020;76:707–714 [PubMed: 32755403]
27. Toth P, Tarantini S, Springo Z, et al. Aging exacerbates hypertension-induced cerebral microhemorrhages in mice: Role of resveratrol treatment in vasoprotection. *Aging Cell.* 2015;14:400–408 [PubMed: 25677910]
28. Nyúl-Tóth Á, Tarantini S, Kiss T, et al. Increases in hypertension-induced cerebral microhemorrhages exacerbate gait dysfunction in a mouse model of alzheimer’s disease. *Geroscience.* 2020;42:1685–1698 [PubMed: 32844283]
29. Poels MM, Ikram MA, van der Lugt A, et al. Cerebral microbleeds are associated with worse cognitive function: The rotterdam scan study. *Neurology.* 2012;78:326–333 [PubMed: 22262748]

30. van Dinther M, Voorter PH, Jansen JF, et al. Assessment of microvascular rarefaction in human brain disorders using physiological magnetic resonance imaging. *J Cereb Blood Flow Metab.* 2022;42:718–737 [PubMed: 35078344]
31. Toth P, Tucsek Z, Sosnowska D, et al. Age-related autoregulatory dysfunction and cerebrovascular injury in mice with angiotensin ii-induced hypertension. *J Cereb Blood Flow Metab.* 2013;33:1732–1742 [PubMed: 23942363]
32. Rizzoni D, De Ciuceis C, Porteri E, et al. Altered structure of small cerebral arteries in patients with essential hypertension. *J Hypertens.* 2009;27:838–845 [PubMed: 19300112]
33. Schimpf C, Teebken OE, Wilhelmi M, Duffield JS. The role of pericyte detachment in vascular rarefaction. *J Vasc Res.* 2014;51:247–258 [PubMed: 25195856]
34. Brown WR, Thore CR. Review: Cerebral microvascular pathology in ageing and neurodegeneration. *Neuropathol Appl Neurobiol.* 2011;37:56–74 [PubMed: 20946471]
35. Hughes AD, Martinez-Perez E, Jabbar AS, et al. Quantification of topological changes in retinal vascular architecture in essential and malignant hypertension. *J Hypertens.* 2006;24:889–894 [PubMed: 16612251]
36. Jordão MT, Ceroni A, Michelini LC. Perfusion of brain preautonomic areas in hypertension: Compensatory absence of capillary rarefaction and protective effects of exercise training. *Front Physiol.* 2021;12:773415 [PubMed: 34975525]
37. Freitas F, Estado V, Reis P, et al. Acute simvastatin treatment restores cerebral functional capillary density and attenuates angiotensin ii-induced microcirculatory changes in a model of primary hypertension. *Microcirculation.* 2017;24
38. van Dinther M, Bennett J, Thornton GD, et al. Evaluation of microvascular rarefaction in vascular cognitive impairment and heart failure (crucial): Study protocol for an observational study. *Cerebrovasc Dis Extra.* 2023;13:18–32 [PubMed: 36646051]
39. Schaeffer S, Iadecola C. Revisiting the neurovascular unit. *Nat Neurosci.* 2021;24:1198–1209 [PubMed: 34354283]
40. de Montgolfier O, Pinçon A, Pouliot P, et al. High systolic blood pressure induces cerebral microvascular endothelial dysfunction, neurovascular unit damage, and cognitive decline in mice. *Hypertension.* 2019;73:217–228 [PubMed: 30571552]
41. Tarantini S, Hertelendy P, Tucsek Z, et al. Pharmacologically-induced neurovascular uncoupling is associated with cognitive impairment in mice. *J Cereb Blood Flow Metab.* 2015;35:1871–1881 [PubMed: 26174328]
42. Hinzman JM, Andaluz N, Shutter LA, et al. Inverse neurovascular coupling to cortical spreading depolarizations in severe brain trauma. *Brain.* 2014;137:2960–2972 [PubMed: 25154387]
43. Kang EJ, Prager O, Lublinsky S, et al. Stroke-prone salt-sensitive spontaneously hypertensive rats show higher susceptibility to spreading depolarization (sd) and altered hemodynamic responses to sd. *J Cereb Blood Flow Metab.* 2023;43:210–230 [PubMed: 36329390]
44. Cipolla MJ. *The cerebral circulation.* San Rafael (CA): Morgan & Claypool Life Sciences; 2016.
45. Santisteban MM, Iadecola C. Hypertension, dietary salt and cognitive impairment. *J Cereb Blood Flow Metab.* 2018;38:2112–2128 [PubMed: 30295560]
46. Saleem M, Herrmann N, Dinoff A, et al. Association between endothelial function and cognitive performance in patients with coronary artery disease during cardiac rehabilitation. *Psychosom Med.* 2019;81:184–191 [PubMed: 30383709]
47. Nezu T, Hosomi N, Aoki S, et al. Endothelial dysfunction is associated with the severity of cerebral small vessel disease. *Hypertens Res.* 2015;38:291–297 [PubMed: 25672660]
48. Longden TA, Dabertrand F, Koide M, et al. Capillary k(+)-sensing initiates retrograde hyperpolarization to increase local cerebral blood flow. *Nat Neurosci.* 2017;20:717–726 [PubMed: 28319610]
49. Koide M, Harraz OF, Dabertrand F, et al. Differential restoration of functional hyperemia by antihypertensive drug classes in hypertension-related cerebral small vessel disease. *J Clin Invest.* 2021;131
50. Vanlandewijck M, He L, Mae MA, et al. A molecular atlas of cell types and zonation in the brain vasculature. *Nature.* 2018;554:475–480 [PubMed: 29443965]

51. Biancardi VC, Son SJ, Ahmadi S, et al. Circulating angiotensin ii gains access to the hypothalamus and brain stem during hypertension via breakdown of the blood-brain barrier. *Hypertension*. 2014;63:572–579 [PubMed: 24343120]
52. Nakagawa T, Hasegawa Y, Uekawa K, et al. Renal denervation prevents stroke and brain injury via attenuation of oxidative stress in hypertensive rats. *J Am Heart Assoc*. 2013;2:e000375 [PubMed: 24125845]
53. Santisteban MM, Ahn SJ, Lane D, et al. Endothelium-macrophage crosstalk mediates blood-brain barrier dysfunction in hypertension. *Hypertension*. 2020;76:795–807 [PubMed: 32654560]
54. Mayhan WG, Faraci FM, Heistad DD. Mechanisms of protection of the blood-brain barrier during acute hypertension in chronically hypertensive rats. *Hypertension*. 1987;9:iii101–105 [PubMed: 3596775]
55. Mayhan WG, Faraci FM, Heistad DD. Disruption of the blood-brain barrier in cerebrum and brain stem during acute hypertension. *Am J Physiol*. 1986;251:H1171–1175 [PubMed: 3098113]
56. Nation DA, Sweeney MD, Montagne A, et al. Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. *Nat Med*. 2019;25:270–276 [PubMed: 30643288]
57. Montagne A, Barnes SR, Sweeney MD, et al. Blood-brain barrier breakdown in the aging human hippocampus. *Neuron*. 2015;85:296–302 [PubMed: 25611508]
58. Dankbaar JW, Hom J, Schneider T, et al. Age- and anatomy-related values of blood-brain barrier permeability measured by perfusion-ct in non-stroke patients. *J Neuroradiol*. 2009;36:219–227 [PubMed: 19251320]
59. Dobrynina LA, Shantieva KV, Kremneva EI, et al. Daily blood pressure profile and blood-brain barrier permeability in patients with cerebral small vessel disease. *Sci Rep*. 2022;12:7723 [PubMed: 35545641]
60. Claassen J, Thijssen DHJ, Panerai RB, Faraci FM. Regulation of cerebral blood flow in humans: Physiology and clinical implications of autoregulation. *Physiol Rev*. 2021;101:1487–1559 [PubMed: 33769101]
61. Hall CN, Reynell C, Gesslein B, et al. Capillary pericytes regulate cerebral blood flow in health and disease. *Nature*. 2014;508:55–60 [PubMed: 24670647]
62. Armulik A, Genove G, Mae M, et al. Pericytes regulate the blood-brain barrier. *Nature*. 2010;468:557–561 [PubMed: 20944627]
63. Hartmann DA, Underly RG, Grant RI, et al. Pericyte structure and distribution in the cerebral cortex revealed by high-resolution imaging of transgenic mice. *Neurophotonics*. 2015;2:041402 [PubMed: 26158016]
64. Hill RA, Tong L, Yuan P, et al. Regional blood flow in the normal and ischemic brain is controlled by arteriolar smooth muscle cell contractility and not by capillary pericytes. *Neuron*. 2015;87:95–110 [PubMed: 26119027]
65. Herman IM, Jacobson S. In situ analysis of microvascular pericytes in hypertensive rat brains. *Tissue Cell*. 1988;20:1–12 [PubMed: 3388410]
66. Tagami M, Nara Y, Kubota A, et al. Ultrastructural changes in cerebral pericytes and astrocytes of stroke-prone spontaneously hypertensive rats. *Stroke*. 1990;21:1064–1071 [PubMed: 2368108]
67. Apaydin DC, Zakaruskas-Seth BI, Carnevale L, et al. Interferon- γ drives macrophage reprogramming, cerebrovascular remodeling, and cognitive dysfunction in a zebrafish and a mouse model of ion imbalance and pressure overload. *Cardiovasc Res*. 2023;119:1234–1249 [PubMed: 36536484]
68. Matsugi T, Chen Q, Anderson DR. Contractile responses of cultured bovine retinal pericytes to angiotensin ii. *Arch Ophthalmol*. 1997;115:1281–1285 [PubMed: 9338674]
69. Kuroda J, Ago T, Nishimura A, et al. Nox4 is a major source of superoxide production in human brain pericytes. *J Vasc Res*. 2014;51:429–438 [PubMed: 25612841]
70. Schröder K, Zhang M, Benkhoff S, et al. Nox4 is a protective reactive oxygen species generating vascular nadph oxidase. *Circ Res*. 2012;110:1217–1225 [PubMed: 22456182]
71. Nishimura A, Ago T, Kuroda J, et al. Detrimental role of pericyte nox4 in the acute phase of brain ischemia. *J Cereb Blood Flow Metab*. 2016;36:1143–1154 [PubMed: 26661159]
72. Nortley R, Korte N, Izquierdo P, et al. Amyloid β oligomers constrict human capillaries in alzheimer's disease via signaling to pericytes. *Science*. 2019;365

73. Yuan X, Wu Q, Liu X, et al. Transcriptomic profile analysis of brain microvascular pericytes in spontaneously hypertensive rats by rna-seq. *Am J Transl Res.* 2018;10:2372–2386 [PubMed: 30210677]
74. Tran CHT, Peringod G, Gordon GR. Astrocytes integrate behavioral state and vascular signals during functional hyperemia. *Neuron.* 2018;100:1133–1148.e1133 [PubMed: 30482689]
75. Diaz JR, Kim KJ, Brands MW, Filosa JA. Augmented astrocyte microdomain ca(2+) dynamics and parenchymal arteriole tone in angiotensin ii-infused hypertensive mice. *Glia.* 2019;67:551–565 [PubMed: 30506941]
76. Boily M, Li L, Vallerand D, Girouard H. Angiotensin ii disrupts neurovascular coupling by potentiating calcium increases in astrocytic endfeet. *J Am Heart Assoc.* 2021;10:e020608 [PubMed: 34459216]
77. Jorfi M, Maaser-Hecker A, Tanzi RE. The neuroimmune axis of alzheimer’s disease. *Genome Med.* 2023;15:6 [PubMed: 36703235]
78. Bisht K, Okojie KA, Sharma K, et al. Capillary-associated microglia regulate vascular structure and function through panx1-p2ry12 coupling in mice. *Nat Commun.* 2021;12:5289 [PubMed: 34489419]
79. Kerkhofs D, van Hagen BT, Milanova IV, et al. Pharmacological depletion of microglia and perivascular macrophages prevents vascular cognitive impairment in ang ii-induced hypertension. *Theranostics.* 2020;10:9512–9527 [PubMed: 32863942]
80. Liu Y, Jacobowitz DM, Barone F, et al. Quantitation of perivascular monocytes and macrophages around cerebral blood vessels of hypertensive and aged rats. *J Cereb Blood Flow Metab.* 1994;14:348–352 [PubMed: 8113330]
81. Faraco G, Sugiyama Y, Lane D, et al. Perivascular macrophages mediate the neurovascular and cognitive dysfunction associated with hypertension. *J Clin Invest.* 2016;126:4674–4689 [PubMed: 27841763]
82. Drieu A, Du S, Storck SE, et al. Parenchymal border macrophages regulate the flow dynamics of the cerebrospinal fluid. *Nature.* 2022;611:585–593 [PubMed: 36352225]
83. Koundal S, Elkin R, Nadeem S, et al. Optimal mass transport with lagrangian workflow reveals advective and diffusion driven solute transport in the glymphatic system. *Sci Rep.* 2020;10:1990 [PubMed: 32029859]
84. Mortensen KN, Sanggaard S, Mestre H, et al. Impaired glymphatic transport in spontaneously hypertensive rats. *J Neurosci.* 2019;39:6365–6377 [PubMed: 31209176]
85. Lerman LO, Kurtz TW, Touyz RM, et al. Animal models of hypertension: A scientific statement from the american heart association. *Hypertension.* 2019:e87–e120 [PubMed: 30866654]
86. Moss MB, Jonak E. Cerebrovascular disease and dementia: A primate model of hypertension and cognition. *Alzheimers Dement.* 2007;3:S6–15 [PubMed: 19595977]
87. Gattu M, Pauly JR, Boss KL, et al. Cognitive impairment in spontaneously hypertensive rats: Role of central nicotinic receptors. I. *Brain Res.* 1997;771:89–103 [PubMed: 9383012]
88. Inaba S, Iwai M, Furuno M, et al. Continuous activation of renin-angiotensin system impairs cognitive function in renin/angiotensinogen transgenic mice. *Hypertension.* 2009;53:356–362 [PubMed: 19047580]
89. Hartman RE, Kamper JE, Goyal R, et al. Motor and cognitive deficits in mice bred to have low or high blood pressure. *Physiol Behav.* 2012;105:1092–1097 [PubMed: 22154805]
90. Levit A, Cheng S, Hough O, et al. Hypertension and pathogenic hamp independently induce white matter astrocytosis and cognitive impairment in the rat. *Front Aging Neurosci.* 2020;12:82 [PubMed: 32351378]
91. Foulquier S, Namsolleck P, Van Hagen BT, et al. Hypertension-induced cognitive impairment: Insights from prolonged angiotensin ii infusion in mice. *Hypertens Res.* 2018;41:817–827 [PubMed: 30120397]
92. Duchemin S, Belanger E, Wu R, et al. Chronic perfusion of angiotensin ii causes cognitive dysfunctions and anxiety in mice. *Physiol Behav.* 2013;109:63–68 [PubMed: 23103834]
93. Eljovich F, Weinberger MH, Anderson CA, et al. Salt sensitivity of blood pressure: A scientific statement from the american heart association. *Hypertension.* 2016;68:e7–e46 [PubMed: 27443572]

94. Faraco G, Brea D, Garcia-Bonilla L, et al. Dietary salt promotes neurovascular and cognitive dysfunction through a gut-initiated th17 response. *Nat Neurosci.* 2018;21:240–249 [PubMed: 29335605]
95. Powles J, Fahimi S, Micha R, et al. Global, regional and national sodium intakes in 1990 and 2010: A systematic analysis of 24 h urinary sodium excretion and dietary surveys worldwide. *BMJ Open.* 2013;3:e003733
96. Ruiz-Opazo N, Tonkiss J. Genome-wide scan for quantitative trait loci influencing spatial navigation and social recognition memory in dahl rats. *Physiol Genomics.* 2006;26:145–151 [PubMed: 16837653]
97. Jabaris SS, Sumathy H, Girish R, et al. Phosphodiesterase-4 inhibitors ameliorates cognitive deficits in deoxycorticosterone acetate induced hypertensive rats via camp/creb signaling system. *Brain Res.* 2015;1622:279–291 [PubMed: 26168894]
98. Blumenthal JA, Smith PJ, Mabe S, et al. Lifestyle and neurocognition in older adults with cognitive impairments: A randomized trial. *Neurology.* 2019;92:e212–e223 [PubMed: 30568005]
99. Carnevale D, Mascio G, D'Andrea I, et al. Hypertension induces brain β -amyloid accumulation, cognitive impairment, and memory deterioration through activation of receptor for advanced glycation end products in brain vasculature. *Hypertension.* 2012;60:188–197 [PubMed: 22615109]
100. Fan Y, Lan L, Zheng L, et al. Spontaneous white matter lesion in brain of stroke-prone renovascular hypertensive rats: A study from mri, pathology and behavior. *Metab Brain Dis.* 2015;30:1479–1486 [PubMed: 26387009]
101. van Rijssel AE, Stins BC, Beishon LC, et al. Effect of antihypertensive treatment on cerebral blood flow in older adults: A systematic review and meta-analysis. *Hypertension.* 2022;79:1067–1078 [PubMed: 35193363]
102. Ding J, Davis-Plourde KL, Sedaghat S, et al. Antihypertensive medications and risk for incident dementia and alzheimer's disease: A meta-analysis of individual participant data from prospective cohort studies. *Lancet Neurol.* 2020;19:61–70 [PubMed: 31706889]
103. Mazure CM, Swendsen J. Sex differences in alzheimer's disease and other dementias. *Lancet Neurol.* 2016;15:451–452 [PubMed: 26987699]
104. Ghazi L, Annabathula RV, Bello NA, et al. Hypertension across a woman's life cycle. *Curr Hypertens Rep.* 2022;24:723–733 [PubMed: 36350493]
105. Orshal JM, Khalil RA. Gender, sex hormones, and vascular tone. *Am J Physiol Regul Integr Comp Physiol.* 2004;286:R233–249 [PubMed: 14707008]
106. Novella S, Heras M, Hermenegildo C, Dantas AP. Effects of estrogen on vascular inflammation: A matter of timing. *Arterioscler Thromb Vasc Biol.* 2012;32:2035–2042 [PubMed: 22679310]

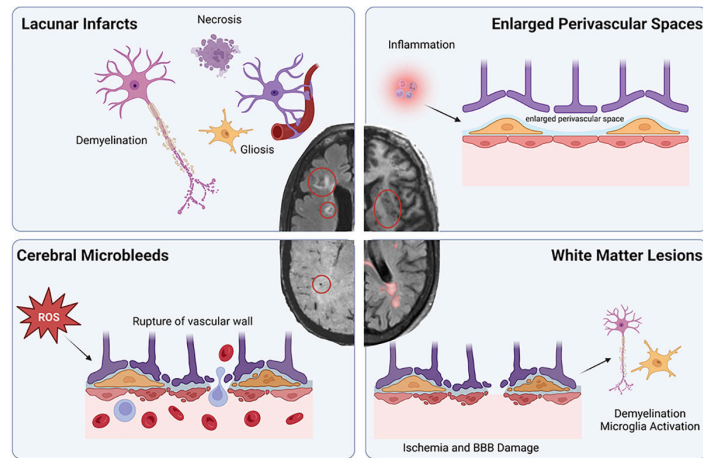


Figure 1. Cerebral small vessel disease manifestations in hypertension.

White matter lesions are visualized as white densities on FLAIR MRIs, and may result from ischemia and breakdown of the blood-brain barrier (BBB) leading to loss of oligodendrocytes, demyelination of neurons, and microglia activation. Lacunar infarcts are found on FLAIR MRIs and contain necrotic waste and have evidence of gliosis, myelin loss, and neuronal loss. Enlarged perivascular spaces are CSF filled spaces that can be seen on T2-weighted MRIs. Inflammation results in the enlargement of these spaces. Cerebral microbleeds, visualized as small circular depositions of blood in SWI MRIs. Studies suggest increased oxidative stress leads to weakening of the microvessels allowing them to rupture in response to the increased pressure. FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging; BBB, blood brain barrier; CSF, cerebral spinal fluid; ROS, reactive oxygen species, SWI, susceptibility weighted imaging.

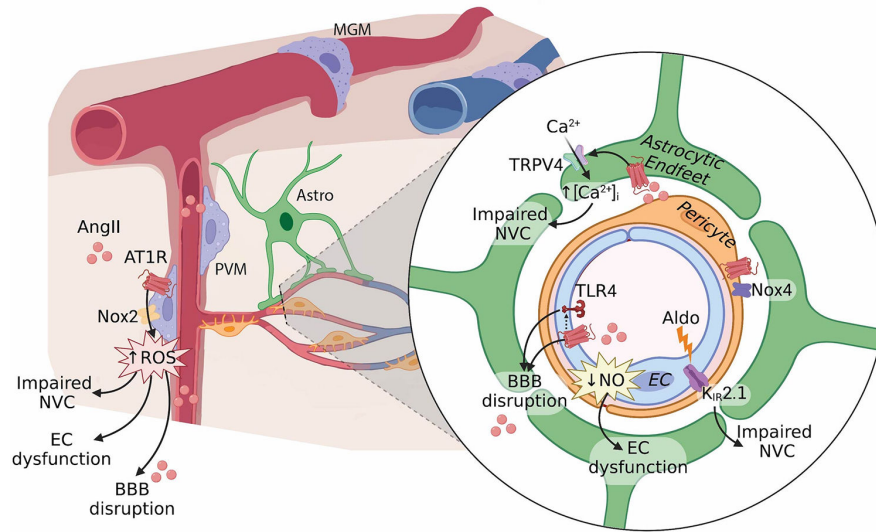


Figure 2. Hypertension impairs the function of the neurovascular unit.

Hypertension affects all cell-types of the neurovascular unit via various mechanisms resulting in endothelial cell (EC) dysfunction, BBB disruption, and impaired neurovascular coupling (NVC). Endothelial dysfunction may result from reduced nitric oxide (NO) bioavailability, resulting from impaired eNOS function and increased ROS production by perivascular macrophages (PVM). Angiotensin II (AngII) type 1 receptor (AT1R) activation in both EC and PVM, and a potential interaction with toll-like receptor 4 (TLR4) in EC, contribute to disruption of the blood-brain barrier (BBB). Neurovascular coupling is impaired by PVM-derived ROS, aldosterone (Aldo)-induced damage of $K_{IR}2.1$ channels and endothelial hyperpolarization, as well as altered calcium signaling in astrocytic endfeet. Pericytes express Nox4 which is upregulated by AngII and may contribute to vascular inflammation. AngII, angiotensin II; $K_{IR}2.1$, inwardly rectifying potassium channel 2.1; Nox, NADPH oxidase; TRPV4, transient receptor potential vanilloid 4; Nox2, NADPH oxidase 2.