Hypertension

REVIEW

Hypertension, Neurodegeneration, and Cognitive Decline

Anthony Pacholko, Costantino Iadecola

ABSTRACT: Elevated blood pressure is a well-established risk factor for age-related cognitive decline. Long linked to cognitive impairment on vascular bases, increasing evidence suggests a potential association of hypertension with the neurodegenerative pathology underlying Alzheimer disease. Hypertension is well known to disrupt the structural and functional integrity of the cerebral vasculature. However, the mechanisms by which these alterations lead to brain damage, enhance Alzheimer pathology, and promote cognitive impairment remain to be established. Furthermore, critical questions concerning whether lowering blood pressure by antihypertensive medications prevents cognitive impairment have not been answered. Recent developments in neurovascular biology, brain imaging, and epidemiology, as well as new clinical trials, have provided insights into these critical issues. In particular, clinical and basic findings on the link between neurovascular dysfunction and the pathobiology of neurodegeneration have shed new light on the overlap between vascular and Alzheimer pathology. In this review, we will examine the progress made in the relationship between hypertension and cognitive impairment and, after a critical evaluation of the evidence, attempt to identify remaining knowledge gaps and future research directions that may advance our understanding of one of the leading health challenges of our time. ***(Hypertension.* 2024;81:991–1007. DOI: 10.1161/HYPERTENSIONAHA.123.21356.)** •

Key Words: Alzheimer disease ■ blood pressure ■ brain ■ hypertension ■ stroke

The impacts of elevated blood pressure (BP) on brain health significantly contribute to cognitive decline over the life course.[1–3] Although associations between chronically elevated BP and cognitive impairment were noted by the end of the 19th century, systematic investigations into the relationship did not begin in earnest until the 1940s to 1960s. The introduction of the Kety and Schmidt[4] method to measure cerebral blood flow (CBF) led to the discovery that cerebrovascular resistance is increased in hypertensives and correlates with hypertensive retinopathy.[5] Shortly thereafter, pioneering observations of diminished psychomotor speed in hypertensive air traffic controllers by Spieth[6] and intellectual decline in patients with hypertension by Wilkie and Eisdorfer[7] provided the initial evidence associating chronically elevated BP with worsened cognition.

More recently, hypertension has emerged as a pathogenic factor both in cognitive impairment on vascular bases and in Alzheimer disease (AD).[8] This hypertension-dementia relationship has led to hypertension being targeted as a treatable condition that could delay the onset of cognitive deterioration. Longitudinal studies indicate preservation of cognition following adequate BP control,[9] particularly in intensive lowering regimens,[10] although such outcomes are not universally observed.[11] Results from investigations into the differential efficacy of antihypertensive agents in combating cognitive decline are similarly conflicting.[12–14] Consequently, emphasis has been placed on the identification of early biomarkers of hypertension-induced brain damage and novel therapeutic targets. To this end, recent studies have focused on identifying the white matter tracts and brain regions affected in hypertension, the mechanisms by which hypertension impairs cognition, and the nature of the association of hypertension with AD pathology.

The American Heart Association celebrates its 100th anniversary in 2024. This article is part of a series across the entire AHA Journal portfolio written by international thought leaders on the past, present, and future of cardiovascular and cerebrovascular research and care. To explore the full Centennial Collection, visit https://www.ahajournals.org/centennial

Correspondence to: Costantino Iadecola, Feil Family Brain and Mind Research Institute, Weill Cornell Medicine, 407 E 61st St, RR-303, New York, NY 10065. Email coi2001@med.cornell.edu

For Sources of Funding and Disclosures, see page 1003.

Hypertension is available at www.ahajournals.org/journal/hyp

Nonstandard Abbreviations and Acronyms

Aβ	amyloid-β
AD	Alzheimer disease
AngII	angiotensin II
AQP4	aquaporin 4
ARB	angiotensin receptor blocker
AT1R	AngII type 1 receptor
BBB	blood-brain barrier
BP	blood pressure
BPV	blood pressure variability
CBF	cerebral blood flow
CSF	cerebrospinal fluid
DBP	diastolic blood pressure
IL-17	interleukin 17
IL-17RA	interleukin-17 receptor A
LRP1	lipoprotein receptor-related protein 1
MAP	mean arterial pressure
MRI	magnetic resonance imaging
PET	positron emission tomography
p-tau	phosphorylated tau
PVM	perivascular macrophage
PVS	perivascular space
RAGE	receptor for advanced glycation end products
SBP	systolic blood pressure
SHR	spontaneously hypertensive rat
SVD	small vessel disease
WML	white matter lesion

The present review will explore the consequences of hypertensive sequelae on cerebrovascular health, cognition, and dementia risk; the associations between hypertension and AD pathology; and potential therapeutic targets and strategies to mitigate the impacts of hypertension on cognitive decline. Finally, we will attempt to highlight outstanding questions that remain unaddressed.

HYPERTENSION AND COGNITIVE DECLINE: EPIDEMIOLOGICAL EVIDENCE

BP trends over the life course, as observed in the Framingham Heart Study,[15] suggest an age-related pattern of systolic BP (SBP) and diastolic BP (DBP) changes in hypertension. Characterized initially by increasing DBP and SBP in early adulthood, DBP falls in late-life concurrent with continual elevation of SBP. Accordingly, mean arterial pressure progressively increases until reaching an asymptote around the seventh decade, whereas pulse pressure, beginning in middle-age, steadily rises throughout the remaining lifespan.[15]

The hypertension-cognition relationship changes over the life course (for in-depth reviews, see References [16,17]). Thus, elevated BP in the fourth to fifth decade of life is associated with late-life cognitive deterioration,[1–3] whereas a U-shaped relationship is noted in the elderly where both high and low BP portend cognitive impairment.[18] Of interest, elevated SBP through mid-life followed by a rapid drop in late-life is associated with severe cognitive decline[19] and brain atrophy,[20] suggesting that late-life reductions in BP may be driven by pathological brain changes impacting autonomic control, as has been advocated for AD.[21] Whether preventing such late-life BP decline would be beneficial remains to be established.

BP variability (BPV), defined as variations in BP stratified by very short-term (beat-to-beat), short-term (24 hours), mid-term (day-to-day), or long-term (visit-to-visit)[22] variability, has emerged as an additional contributor to cognitive impairment, particularly in the elderly. In recent meta-analyses combining 53 (9 very short-, 12 short-, 9 mid-, and 23 long-term) and 19 (4 short-, 4 mid-, 11 long-term) studies, worse cognitive performance was associated with short-, medium-, and long-term BPV.[23,24] In contrast, low BPV over the very short term elevates the risk of poor cognitive outcomes, perhaps due to impairment of the ability to adjust perfusion commensurate with demand (eg, postural changes).[23]

In summary, hypertension, particularly in mid-life, is associated with worse long-term cognitive outcomes, and increased short-, mid-, and long-term BPV are emergent risk factors for cognitive decline and dementia, especially in the elderly.

HYPERTENSION AND THE PATHOBIOLOGY OF CEREBROVASCULAR IMPAIRMENT

In this section, we will first review basic concepts on the blood supply of the brain, and then examine the consequences of hypertension on the structure and function of cerebral vessels.

Cerebral Blood Supply and the Neurovasculome

The carotid arteries enter the skull and merge to form the circle of Willis, a collateral flow loop from which the anterior, middle, and posterior cerebral arteries originate.[25] Branches of these vessels travel along the surface of the brain within the subarachnoid space, forming an anastomotic network (pial arteries),[25] before diving into the substance of the brain (penetrating arteries and arterioles) while ensheathed within an extension of the subarachnoid space delimited by the vascular basement membrane and glia limitans (perivascular space; PVS). As these penetrating arterioles advance into the brain

parenchyma, the PVS disappears, and the vascular basal lamina and glia limitans merge.[25] At this level, arterioles are surrounded by a single layer of smooth muscle cells which, as the vessels get smaller, become discontinuous until replaced by pericytes at the capillary level.[25]

Interactions between cerebral vessels and neural elements are crucial determinants of CBF. Structural and functional associations between vascular cells, glia, and neurons, dubbed the neurovascular unit, regulate blood-brain barrier (BBB) maintenance, and the adjustment of cerebral perfusion commensurate with local metabolic demands.[25] Owing to the segmental specificity of these neurovascular interactions, the concept of the neurovascular unit has been recently expanded to include large extracerebral and intracerebral vessels, as well as meningeal vessels and lymphatics (the neurovasculome).[26]

Hypertension Alters Cerebrovascular Structure

Hypertension is often preceded by arterial stiffening[27] which, as a result of diminished vascular compliance, drives an elevation in pulse pressure[27] that exposes the downstream circulation to increased tensile strain,[28] triggering adaptive remodeling responses throughout the cerebrovascular tree in an attempt to preserve vessel integrity (Figure 1).[16,29] Remodeling is defined as inward or outward depending on whether luminal diameters increase or decrease, and eutrophic or hypertrophic based on the nature of changes to the vascular wall. Eutrophic remodeling is characterized by an altered luminal diameter sans modification of wall thickness,[29] whereas increased wall thickness consequent to cellular hyperplasia/hypertrophy and deposition of extracellular matrix signifies hypertrophic remodeling.[29] Although indeterminate, stiffening and remodeling involve the convergence of hemodynamic stress, endothelial dysfunction, immune infiltration, and inflammation,[30,31] as well as the actions of overlapping mediators, such as cytokines, AngII (angiotensin-II), endothelin, and oxidative stress.[32]

Large Extracranial and Intracranial Cerebral Arteries

Hypertension contributes to the formation of atherosclerotic plaques in both extracranial and intracranial cerebral arteries,[16,33] increasing the risk of ischemic stroke.[34,35] Extracranial lesions are characterized by elevated accumulation of lipids in vertebral and carotid arteries,[36] increasing the risk for artery-to-artery embolism,[36] whereas intracranial lesions affecting the circle of Willis and its branches display a fibrous expression more likely to result in local vascular occlusion.[34] How hypertension promotes atherosclerosis remains incompletely

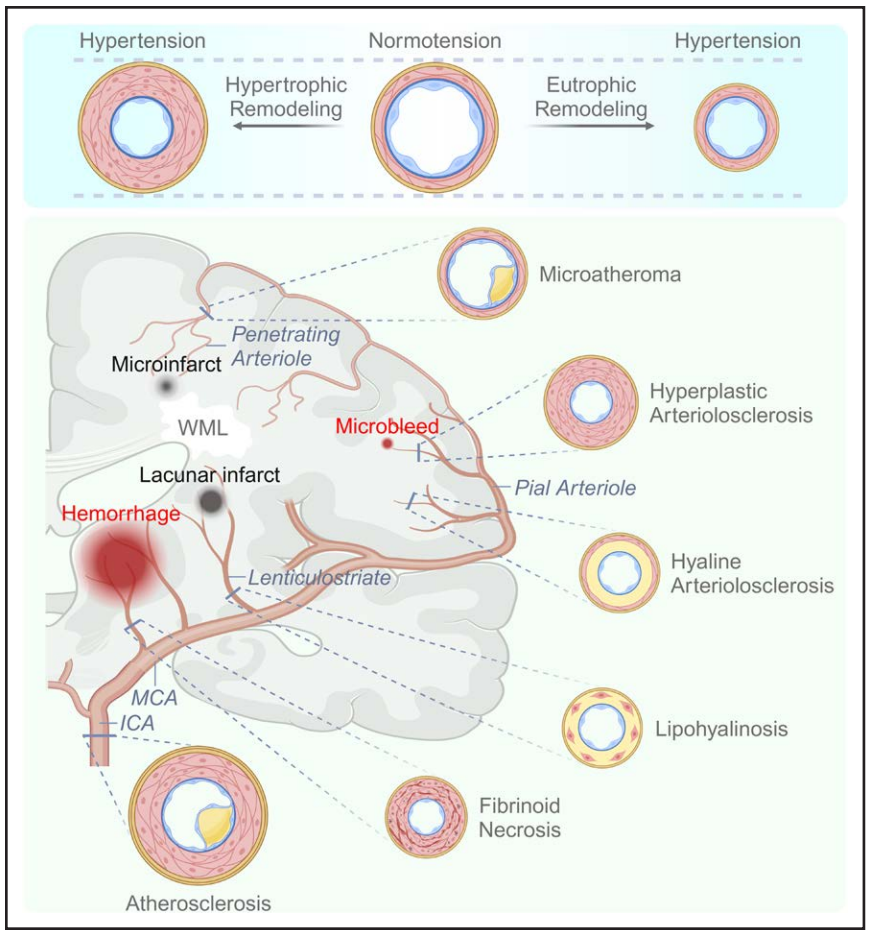

Figure 1. Structural alterations and segmental pathology induced by hypertension.
Top, Vascular remodeling proceeds in either an outward or inward manner in response to mechanical, cellular, inflammatory, and oxidative factors. **Bottom**, The predominant vascular structural alterations associated with hypertension are indicated according to the affected segment of the neurovasculature. Key pathological outcomes are also depicted. Details are provided in the text. ICA indicates internal carotid artery; MCA, middle cerebral artery; and WML, white matter lesion.

understood, but AngII is thought to contribute by generating reactive oxygen species and upregulating cytokines, chemokines, and growth factors.[37] The resultant cellular and molecular milieu triggers an inflammatory response in the vascular wall that precipitates endothelial dysfunction, neointima formation, and atherosclerotic lesions.[37]

In addition to atherosclerosis, concurrent vascular stiffening and stenosis resulting from sclerosis of the vascular wall (arteriosclerosis) negatively affect the cerebral blood supply and downstream microvasculature. These changes are implicated in CBF reduction[38]; diminution of cerebrovascular reserves,[39] which can elevate stroke risk[40]; and increased hydrodynamic impacts on the microvasculature.[41] Modification of the extracellular matrix is a major contributor to arterial stiffening and is characterized, in part, by collagen and fibronectin accumulation, metalloprotease-mediated elastin fragmentation, and pro-fibrotic cascades related to transforming growth factor-β.[30]

Pial Vessels and Penetrating Arterioles

Pial and penetrating arteries and arterioles are uniquely sensitive to chronic elevations in BP.[16] In humans, hypertension-induced microatheroma in pial arteries and small perforating arteries (300–800 μm external diameter[42–44]) can occlude vessels and instigate lacunar infarction or microinfarction.[44] Moving further into the brain, small penetrating arteries and arterioles, from 300 to 20 μm,[42–44] arising from either the first segment of the middle cerebral artery or terminal branches of the pial arteries, converge on deep white matter territories.[16] As these vessels display vulnerability to shifts in upstream pressure, scant collateralization, and limited anastomosis,[16] they are strongly implicated in formation of the white matter damages attendant to vascular dysfunction.[45,46]

Three vascular lesions predominate within these smaller vessels: lipohyalinosis, fibrinoid necrosis, and arteriolosclerosis. Lipohyalinosis involves asymmetrical deposition of an amorphous, glass-like material composed of collagen and degenerated smooth muscle tissue into the vascular wall, whereas fibrinoid necrosis, observed in more advanced lesions, is signified by infiltration of fibrin and its degradation by products.[42–44] More common is arteriolosclerosis,[43] characterized by myocyte degradation and loss of elastin alongside concentric accumulation of fibro-hyaline materials and collagens in the vascular wall, leading to stenosis and reduced elasticity (hyaline arteriolosclerosis),[42–44] or the extensive intimal fibromuscular proliferation, luminal narrowing, and necrotic degeneration often associated with malignant hypertension (hyperplastic arteriolosclerosis).[42–44] Capillaries and precapillary arterioles are also affected, marked by loss of endothelial cells and pericytes (string vessels), increased thickness of the basal lamina and accompanying tortuosity, fibrin deposition, and overall rarefaction.[47]

Collectively, these changes form the basis of hypertension-associated small vessel disease (SVD), a disorder affecting arterioles, venules, and capillaries of the subcortical and periventricular white matter in a segment-specific manner[42–44]; atheromatous lesions are typically observed in larger arteries/arterioles situated upstream of distal perforating vessels supplying the deep parenchymal tissues, which are in turn affected by arteriolosclerosis, lipohyalinosis, and fibrinoid necrosis (Figure 1).[42–44] The sequelae of SVD, detectable via magnetic resonance imaging (MRI), include white matter lesion (WML), small ischemic foci (lacunes and microinfarcts) and microhemorrhages,[48] venous collagenosis,[49] and enlarged PVS.[50] SVD is also influenced by short-term and long-term BPV, evidenced by brain imaging and autopsy data (arteriolosclerosis, microinfarcts, WMLs, enlarged perivascular spaces, and atherosclerosis of the circle of Willis).[51,52]

Hypertension Impairs Cerebrovascular Function

The brain is dependent on a continuous and highly regulated supply of oxygen- and glucose-rich blood. Accordingly, neurovascular mechanisms assure that perfusion is commensurate with the brain's regionally and temporally diverse energetic and waste clearance requirements.[25] In this section, the mechanisms regulating CBF are reviewed, focusing on factors disrupted in hypertension which may lead to cognitive impairment. A more comprehensive description of CBF regulation is found in recent reviews.[25,26,53,54]

Autoregulation

The cerebral vasculature maintains CBF within ≈ ±20 mm Hg of baseline,[53] dampening the BP changes attendant to daily life. Traditionally, autoregulatory responses have been studied using stepwise changes in BP coupled with measurement of CBF; the stabilization of perfusion during these manipulations is known as static autoregulation.[55] In the 1990s, the introduction of transcranial Doppler flowmetry enabled the assessment of flow velocity in response to rapid changes in BP,[56] leading to the characterization of dynamic autoregulation,[57] which refers to the latency between BP changes and corresponding adjustments to vascular resistance.[53] These studies revealed that while rapid fluctuations in BP escape autoregulation and result in flow changes, they are not as large as if the autoregulatory process were absent.

On a cellular level, autoregulation depends on the ability of smooth muscle cells to constrict or dilate in accordance with intravascular pressure (myogenic response). Multiple mechanisms have been implicated, including (1) ion channels and mechanosensors, which adjust intracellular calcium levels commensurate with fluctuating transmural pressures,[58] (2) alteration of contractile apparatus calcium sensitivity,[59] and (3) depolarization-mediated amplification of intracellular calcium signaling.[60]

Animal studies have provided evidence that hypertension shifts the static autoregulatory curve to the right, rendering the brain more susceptible to reductions in BP.[16] In contrast, most human studies suggest that both static and dynamic autoregulation are preserved among hypertensives,[53] except for malignant hypertension (SBP, 180–260 mm Hg), where failure of the autoregulation mechanism causes the flow to passively follow BP.[61]

Overall, autoregulation appears to be a resilient mechanism that is largely maintained in human hypertension, but the available data have limitations that need to be considered. Since in most studies flow was assessed in a single vessel by transcranial Doppler, regional changes in dynamic autoregulation could have been missed. Furthermore, the inherent risk associated with lowering BP has been an obstacle to assessing the lower limit of static autoregulation in patients with hypertension.

Neurovascular Coupling

Neurovascular coupling, which pertains to the distribution of blood to active brain regions commensurate with their metabolic demands,[25] requires the participation of all constituents of the neurovascular unit at each level of the cerebrovasculature and is driven by diffusible mediators (NO, prostanoids, adenosine, ions, etc) and segment-specific intrinsic vascular mechanisms.[25] In brief, activation of neurons deep within the brain parenchyma initiates a series of vascular alterations which begin at the level of the capillary endothelium and are transmitted upstream in a retrograde fashion through intramural signaling, resulting in propagation of smooth muscle cell relaxation and attendant vasodilation.[62–64] This retrograde propagation ultimately reaches larger pial vessels, which must relax to facilitate adequate blood flow to the activated region and prevent flow steal from neighboring vascular territories.[25]

At present, a paucity of human studies have examined neurovascular coupling in hypertension. In untreated hypertensives, increased baseline BP is associated with diminished regional alterations to CBF during cognitive tasks.[65] Similar impairments are reported for blood flow responses to visual stimuli in the retina[66] or posterior cerebral artery.[67] These observations, albeit limited, support the presence of impaired functional hyperemia in hypertensives and, in turn, increased susceptibility to vascular insufficiency.

Endothelial Cells: Vasoregulation and the BBB

Cerebrovascular endothelial cells regulate vasomotor tone by releasing vasoactive messengers in response to select chemical and mechanical stimuli.[54] Perhaps the most well-studied endothelium-dependent vasoactive mechanism is NO-mediated vasodilation in response to cholinergic agonists activating endothelial NO synthase.[68] Signaling in a paracrine manner, NO reaches the vascular smooth muscle cells, where it initiates cGMP-mediated relaxation of the smooth muscle.[69] As mentioned above, the cerebral capillary endothelium contributes to functional hyperemia. Release of K^+ by neuronal depolarization activates endothelial inward rectified K^+ channels, leading to a hyperpolarization cascade transmitted upstream through inter-endothelial junctions which, upon reaching smooth muscle cells, culminates in their relaxation.[62]

Endothelial cells are also the site of the BBB.[70] The bidirectional exchange of molecules between blood and brain is regulated by (1) molecular transporters on their surface, which gate substrate entry, (2) tight junctions between adjacent endothelial cells, which largely prevents paracellular solute flux, and (3) paucity of vesicular transport, which limits transcytosis.[70]

In humans, endothelial dysfunction in peripheral arteries precedes BP elevation and correlates with the severity of hypertension postdevelopment.[71] Although direct in vivo evaluation of cerebral endothelial function in humans is not feasible, inhibition of NO synthesis does not attenuate arteriolar blood flow in the retina of patients with hypertension, suggesting NO deficiency concomitant with endothelial dysfunction,[66] and endothelium-dependent vasodilatory responses to acetylcholine are diminished in arteriolar samples collected postmortem from patients with SVD/AD mixed pathology.[72]

These endothelial aberrations may affect cognition: impaired endothelium-dependent vasodilation in peripheral arteries is associated with brain microhemorrhages[73] and WMLs,[74] both of which are implicated in cognitive decline[75,76]; and some patients with hypertension present with BBB impairment, which can contribute to brain damages and SVD (eg, WMLs).[77]

Perivascular Spaces, Waste Clearance, and Neuroimmune Regulation

PVS and the vessels within have emerged as major routes for the elimination of potentially deleterious byproducts of brain activity, such as Aβ (amyloid-β) and tau.[78] Several clearance systems have been proposed.[78] A transvascular pathway facilitates the passage of select molecules through the vascular wall by way of abluminal transporters.[70] Since the brain parenchyma lacks conventional lymphatic vessels, other pathways are thought to use the PVS as a conduit to carry solutes out of the brain. In the perivascular pathway, solutes are thought to exit the parenchyma through retrograde transport along the vascular basal lamina or PVS, eventually mixing with the cerebrospinal fluid (CSF) in the subarachnoid space and draining into the cervical lymph nodes.[79] Running opposed to this route is the glymphatic pathway. Aided by AQP4 (aquaporin-4) water channels in astrocytic end feet, convective and diffusive forces are hypothesized to drive CSF from the periarterial space into the parenchyma, where it blends with the interstitial fluid and picks up waste products. This waste-rich fluid is thought to exit into the perivenous space, travel to the subarachnoid compartment, and drain into the meningeal lymphatics.[80]

Cerebral vessels and PVS are also involved in immune regulation, and the constituent vessels of the cerebrovasculature are surrounded by an assortment of immune cells. Yolk sack-derived myeloid cells, collectively termed border-associated macrophages, populate the meninges, PVS, and choroid plexus,[81] and have emerged as key correlates of the neurovascular and cognitive dysfunction associated with hypertension.[82,83]

In humans, hypertension is linked to enlarged PVS.[84,85] Although incompletely understood, a proposed mechanism invokes hypertension-induced stiffening of large arteries exposing the microvasculature to enhanced pulsatile pressures,[86] which increases the mechanical stress under which the PVS is placed and drives their enlargement.[85] In support, a recent neuroimaging study found that the glymphatic removal of an intravenously administered tracer was reduced in SVD-positive participants, most of whom were hypertensive.[87] This hypertension-clearance dynamic is discussed further in the impaired clearance of amyloid and tau peptides section.

Hypertension and Neurovascular Dysfunction: Mechanistic Studies

Angiotensin II

Arguably the most well-established models of hypertension involve the use of pressor doses of AngII that elicit a sharp increase in BP, or sub-pressor doses (slow-pressor model), which drive a gradual elevation in BP over several days. The slow-pressor model has gained in popularity for its potential to capture the progressive increase in BP of primary hypertension.[88] Neurovascular dysfunction, that is, impaired functional hyperemia and endothelial vasodilation, is provoked by both acute and chronic AngII treatment,[82,89,90] and is driven by the interaction of AngII with one of its receptors, AT1R (AngII receptor type 1), on vascular and perivascular cells (Figure 2),[82,89] as well as brain structures involved in autonomic regulation, such as the subfornical organ and periventricular hypothalamus.[90]

Intriguingly, the effects of AngII on neurovascular function may be independent of BP elevation. Direct neocortical application of AngII, which does not increase BP, elicits neurovascular uncoupling[89]; nonpressor doses of AngII induce neurovascular dysfunction[91]; and topical application of the ARB (AngII receptor blocker) losartan to the neocortex rescues functional hyperemia without lowering BP.[89] Additional evidence for BP independent effects is provided by the BP high mouse [82] and spontaneously hypertensive rat (SHR),[92] genetic models of lifelong hypertension, as well as the deoxycorticosterone acetate+salt (DOCA-salt) model of salt-sensitive hypertension,[93] in which neurovascular dysfunction can be rescued despite increased BP.[82,91,93] Furthermore, elevations

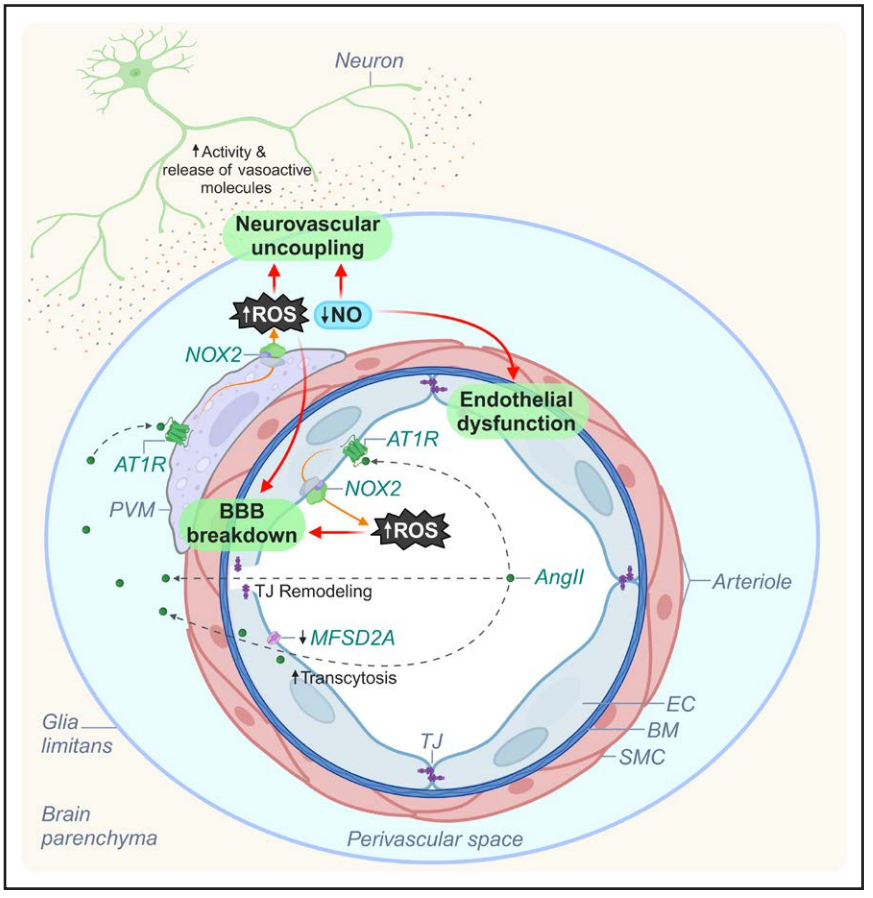

Figure 2. Potential mechanisms of neurovascular dysfunction in AngII (angiotensin II) hypertension. Circulating AngII interacts with AT1R (angiotensin II receptor type I) on endothelial cells to initiate blood-brain-barrier (BBB) disruption (tight junction remodeling and suppression of MFSD2A, leading to increased transcytosis) and enable its entry into the PVS. Next, circulating and brain-derived AngII engage with AT1R on PVM, leading to NOX2 activation, vascular oxidative (superoxide) and nitrosative (peroxynitrite) stress, reduced NO, further BBB disruption, and neurovascular dysfunction. EC indicates endothelial cell; NO, nitric oxide; NOX2, NADPH oxidase 2; PVM, perivascular macrophage; PVS, perivascular space; ROS, reactive oxygen species; SMC, smooth muscle cell; and TJ, tight junction.

in BP provoked by an α-adrenergic agonist fail to induce neurovascular dysfunction,[82] suggesting that not all pressor agents will affect these regulatory mechanisms. Although these experimental observations highlight the BP-independence of neurovascular dysfunction, the pathogenic impacts of elevated BP in human hypertension cannot be underestimated. After all, antihypertensive intervention dramatically lowers stroke risk and,[94] in some studies, improves cognitive function[10,95]; however, as the data on the efficacy of BP lowering against cognitive decline is conflicting (see Therapeutic Interventions), BP-independent effects warrant further consideration.

Cytokines

In recent years, interleukin-17 (IL-17), a proinflammatory molecule, has received increased attention for its contributions to neurovascular dysfunction. In the AngII[96] and DOCA-salt[93] models, IL-17 is required for the development of neurovascular dysfunction and cognitive impairment, whereas neutralization of IL-17,[96] inhibition of its receptor,[96] or elimination of its cellular sources[93] prevents such outcomes. Intriguingly, IL-17 knock-out mice treated with DOCA-salt develop increased BP without neurovascular dysfunction,[93] attesting to the BP-independent effects of hypertension-associated mediators.

Oxidative Stress

Oxidative stress is a principal driver of the cerebrovascular sequelae of hypertension.[16] Although several enzymatic sources have been identified,[97] a NOX2 containing NADPH oxidase appears to be the prime source of the reactive oxygen species involved in neurovascular dysfunction, particularly in AngII-induced hypertension,[82,89] but also in other models, such as salt-sensitive[93] and in BP high mice.[82] Accordingly, both genetic deletion and pharmacological inhibition of NOX2 prevent neurovascular dysfunction and cognitive impairment in models of hypertension.[82,89,93] However, how reactive oxygen species precipitate these alterations requires elucidation. In AngII hypertension, peroxynitrite, a diffusible reaction product of NOX-2-derived superoxide with NO,[98] is the ultimate mediator of the neurovascular dysfunction.[99] Alternative mechanisms may include NO scavenging, and redox modifications of proteins, lipids and DNA, among others.[98]

Innate Immunity: Perivascular Macrophages and Microglia

Perivascular macrophages (PVM) are found closely apposed to the outer vascular wall of intracerebral arterioles and venules within the PVS.[81] PVM express both AT1R and IL-17RA, are richly endowed with the reactive oxygen species producing enzyme NOX2,[100,101] and have emerged as key players in the neurovascular and cognitive dysfunction observed in animal models of hypertension.[82,93] In the slow-pressor model, AngII disrupts the BBB and subsequently enters the PVS, where it interacts with AT1R expressed on PVMs to elicit vascular impairments, as evidenced by the restoration of neurovascular function which follows PVM depletion or deletion of *At1r* or *Nox2* from PVM.[82] The disruption of the BBB is mediated by remodeling of tight junctions and an increase in vesicular transport consequent to suppression of *Mfs2da*,[102] a negative regulator of transcytosis.[103] Although activation of endothelial AT1R initiates the BBB dysfunction, PVMs are required for its full expression (Figure 2).[102] In addition, depletion of PVMs abrogates the neurovascular dysfunction and cognitive impairments attendant to life-long hypertension in BP-high mice,[82] as well as to salt-sensitive hypertension in the DOCA-salt model,[93] supporting the inter-model generalizability of their contributions.

Less is known on the role of microglia. In the slow-pressor model, microglia acquire a proinflammatory phenotype at sites of BBB leakage, and their depletion (along with PVM) by the colony-stimulating factor 1 receptor inhibitor PLX5622 partially curtails cognitive impairments without rescuing BBB integrity.[104] However, how microglia promote cognitive impairment independently of BBB disruption and whether PVMs are also involved remains to be determined.

Adaptive Immunity: T Cells

T cells, namely of the T_h17 (T helper 17) and γδ17 subtypes, and IL-17, their principal effector cytokine,[105] have emerged as crucial players in the induction of hypertension[106] and its sequelae, both centrally[93] and peripherally.[106] Concerning central immunity, a recent study using the DOCA-salt paradigm revealed T-cell-dependent mechanisms of neurovascular dysfunction (Figure 3): in the circulation, IL-17 derived from gut localized and circulating T_h17 and γδ17 cells acts on cerebral endothelial IL-17RA to reduce NO production and disrupt endothelial vasoactivity; in the brain, IL-17 secreted from γδ17 cells situated within the dura acts on IL-17RA in PVMs to induce vascular oxidative stress and concomitant neurovascular uncoupling. Although endothelial IL-17RA deletion partially restores cognition, antagonizing the central sources (T cells) or targets of IL-17 (PVMs) rescues cognition in full,[93] revealing a previously unappreciated involvement of meningeal immunity in the cognitive effects of salt-sensitive hypertension.

HOW DOES HYPERTENSION PROMOTE COGNITIVE DECLINE?

The most profound impacts of hypertension on cognition appear to center on executive function,[2] motor speed, and attention,[107] domains classically associated with vascular cognitive impairment.[16] Typically, memory is involved

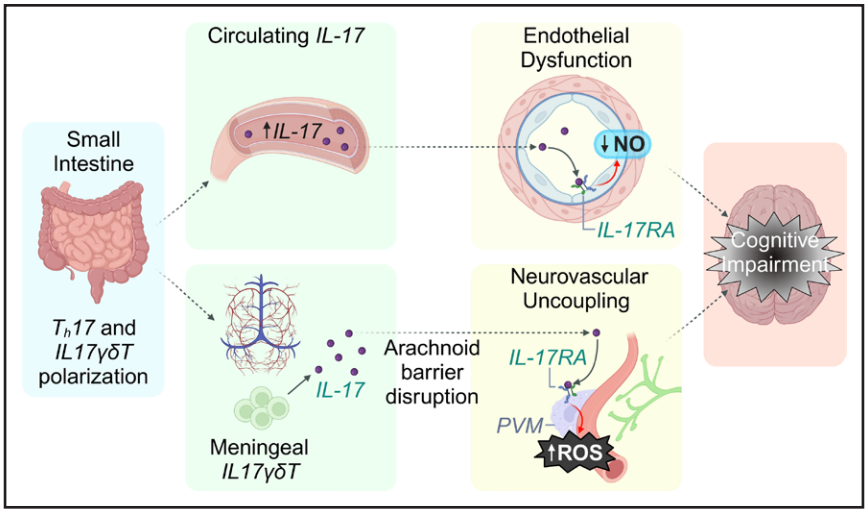

Figure 3. Putative contributions of meningeal immunity to neurovascular dysfunction in salt-sensitive hypertension.
DOCA-salt treatment leads to production of IL-17 (interleukin 17) from T cells in the small intestine and dural immune compartment. Gut-derived circulating IL-17 interacts with IL-17RA on endothelial cells to disrupt endothelial function. IL17 produced in the meninges enters the subarachnoid space, travels to the , perivascular space (PVS), and engages with IL-17RA (IL-17 receptor A) on perivascular macrophage (PVMs) to induce vascular oxidative stress (via NOX2 [NADPH oxidase 2]) and neurovascular dysfunction. EC indicates endothelial cell; IL17γδT, IL-17-producing gamma delta T cell; NO, nitric oxide; ROS, reactive oxygen species; SMC, smooth muscle cell; and T_h17, T helper 17 cell.

more so in AD-related cognitive decline than in vascular cognitive impairment, although this is more of a trend than a rule (see Reference [108]).

In this section, the potential mechanisms underlying hypertension-induced cognitive impairment are discussed, with a particular focus on 2 hallmarks of vascular cognitive impairment: ischemic and hemorrhagic brain lesions and white matter disease.[16]

Ischemia, Hemorrhage, White Matter Lesions, and Atrophy

Hypertension is a major risk factor for both hemorrhagic and ischemic stroke which, in turn, is associated with a 3-6-fold increased risk of cognitive impairment.[16] Lacunar infarcts, microinfarcts, and microbleeds similarly portend cognitive deterioration.[109–111]

WMLs are among the most common lesions associated with hypertension.[112] SVD, often a consequence of hypertension,[113] is a major contributor to WML burden,[114] and associations between SVD, WML, and cognitive decline have been reported in the epidemiological literature. In the Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Cohort, baseline SVD severity and progression were independently correlated with dementia risk over 14 years[115]; SVD progression over time was accelerated by baseline vascular risk factors, a phenomenon primarily driven by hypertension[116]; and reduced processing speed was associated with WML load.[75] Supporting these observations, WML risk loci overlapped with BP traits in a meta-analysis of genome-wide association studies, with subsequent Mendelian randomization suggesting a causal association of WML volume with genetically predicted SBP.[117]

Mechanistically, hypoxia-ischemia following occlusion or rarefaction of the microvessels supplying the subcortical white matter likely contributes to white matter disease consequent to SVD.[16,118] Indeed, reduced cerebrovascular reactivity to CO_2 was observed to precede the progression of normal-appearing white matter to WML in middle-aged subjects with moderate-to-severe WML burden at baseline[119]; arteriolosclerosis and a hypoxic milieu have been found in WMLs postmortem[120]; and increased severity of arteriolosclerosis in watershed regions located between arterial territories has been shown to associate with greater WML and neurofibrillary tangles at autopsy.[121] However, reverse causation has been suggested[122] wherein reductions in blood supply could be consequent to BBB dysfunction-induced damage of the microvasculature via extravasation of neurotoxic molecules, edema, and microvascular compression,[123] or by WMLs lowering local CBF requirements secondary to deafferentation, tissue atrophy, and reduced energy demands.[124]

Disrupted Functional Connectivity

Hypertension-induced loss of white matter integrity and consequent derangement of functional connectivity may affect cognition. Continued progression of WMLs,[125] microstructural alterations,[126] and network functional deficits[127,128] correlate with cognitive decline in patients with hypertension.[126–128] In recent years, location-based image analyses have revealed that strategically placed WMLs are particularly relevant to cognitive decline.[110] In a study employing white matter tractography and resting state functional MRI,[126] hypertension was associated with early alterations in the superior longitudinal

fasciculus, the forceps minor, and the anterior thalamic radiation. Patients with hypertension performed worse in the domains ascribable to these affected tracts in subsequent cognitive testing (executive functions, processing speed, and memory).[126] These observations are corroborated by an analysis combining imaging in middle-aged adults from the UK Biobank cohort with genetic causal inference approaches, which found elevated SBP to associate with alterations to the external capsule, anterior corona radiata, and anterior thalamic radiation, the latter 2 of which are linked to cognitive decline.[129]

POTENTIAL CONTRIBUTIONS OF HYPERTENSION TO AD

Once considered to be purely a neurodegenerative disease, an increasing body of evidence indicates the involvement of vascular brain lesions in AD, such that most cases diagnosed clinically present mixed vascular and AD pathologies.[8,130] Relative to age-matched controls, AD brains display elevated intracranial atherosclerosis and numerous microvascular alterations.[131] Furthermore, BBB permeability is increased[132] and hemodynamic responses to neuronal activity are suppressed[133] in the prodromal period, implicating vascular factors early in disease progression.

Epidemiological Associations of Hypertension With AD Biomarkers

Amyloid positron emission tomography (PET) data concerning the link between amyloid pathology and hypertension are conflicting. In the ARIC cohort, heightened vascular risk factor burden in mid-life was associated with elevated PET Aβ in old age; however, hypertension alone did not significantly correlate with amyloid burden.[134] In the British 1946 birth cohort, increased BP in middle age associated with late-life WML burden and brain atrophy, but not PET Aβ.[135] Although these findings suggest that hypertension fails to exacerbate Aβ burden, this does not preclude the possibility that amyloid pathology in some of the patients with hypertension was driven, in part, by vascular contributions. Of note, the impact of hypertension on Aβ may be modulated by genetic risk factors. In carriers of the ε4 allele of the apolipoprotein E gene, mid-life vascular burden correlated with increased brain amyloid in ARIC participants at 20-year follow-up,[134] whereas in the Rotterdam study, hypertension was associated with Aβ burden 7 years after initial assessment.[136]

As for tau, increased pulsatility secondary to aortic stiffness correlated with tau burden in the rhinal and entorhinal cortices of dementia-free subjects from the Framingham Heart Study,[137] and a clear age-related pattern of BP was delineated in the Chinese Alzheimer's Biomarker and LifestylE cohort, where higher mid-life SBP, late-life lower DBP, and increased pulse pressure in both mid and late life was associated with tau-related biomarkers and cognitive dysfunction, but not amyloid burden.[138]

Intriguingly, inconsistencies in BP might be important for both amyloid and tau pathologies. An association of BPV with phosphorylated tau (p-tau) and decreased Aβ was observed in the CSF of older participants from the Alzheimer Disease Neuroimaging Initiative.[139]

Overall, these observations present a plausible association of hypertension with AD pathology, particularly at the level of tau, although it remains unclear whether this relation is causative or incidental, or if the effects of hypertension on cognition involve or simply co-occur with AD pathology.

Hypertension and AD Pathology: Mechanistic Considerations

Amyloidogenesis and Tau Hyperphosphorylation

Hypertension promotes tau hyperphosphorylation and Aβ accumulation in animal models (Figure 4). In transgenic models of brain amyloid build up, AngII-induced hypertension increases Aβ deposition[140] and p-tau immunoreactivity.[141] Similar findings are reported in other models, such as SHR.[142] Although the underlying mechanisms have yet to be elucidated, AngII-induced elevation of β-[140] and γ-secretase[143] activity, which shifts APP processing toward β-amyloidogenesis, could be involved. Experimentally, genetic ablation of AT1R curtails γ-secretase activity and subsequent Aβ generation,[143] and AT1R blockers abrogate amyloid pathology: telmisartan reduces Aβ formation in stroke-resistant SHR[144] and valsartan diminishes Aβ burden in Tg2576 mice.[145] Regarding tauopathies, AngII[146] and IL-17[93,147] disrupt endothelial NO synthase-mediated NO production and reduce NO bioavailability. Since suppression of endothelial NO has been linked to tau phosphorylation via activation of cyclin-dependent kinase 5,[141] AngII and IL-17 could promote p-tau through this mechanism, although supporting evidence is missing.

Impaired Clearance of Amyloid and Tau Peptides

Aβ clearance is facilitated by the glymphatic and perivascular pathways,[148,149] as well as utilization of transporters situated within the BBB, namely the low-density LRP1 (lipoprotein receptor-related protein 1) for egress and the receptor for advanced glycation end products (RAGE) for ingress[70]; thus, disruption of these systems would be expected to worsen amyloid accumulation.

Hypertension-induced alterations in perivascular pumping, a fluid transport mechanism wherein vascular wall kinetics drive CSF flow in the PVS,[150] could aggravate

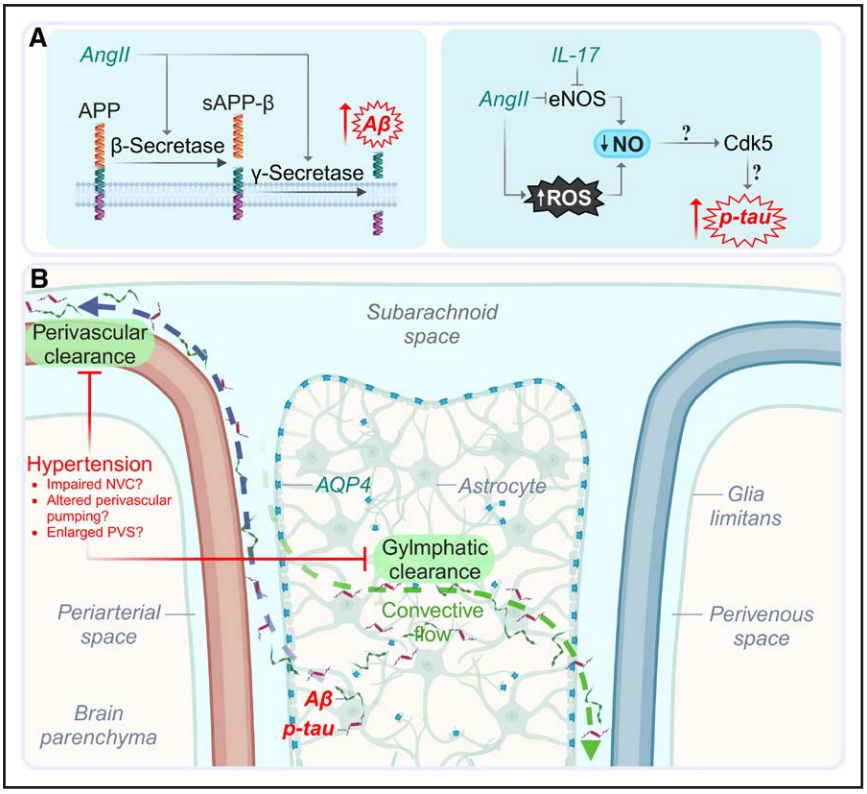

Figure 4. Potential mechanisms associating hypertension and Alzheimer desease (AD).
The oxidative and inflammatory sequela of hypertension could promote AD pathology by increasing Aβ (amyloid-β) and phosphorylated tau (p-tau) (**A**), and disrupting perivascular and glymphatic clearance (**B**). Hypertension may enhance Aβ accumulation through increased processing of APP (amyloid precursor protein) by secretase enzymes. Tau phosphorylation may be elevated under hypertensive conditions consequent to reductions in endothelial NO bioavailability and attendant activation of cyclin-dependent kinase 5. AngII indicates angiotensin II; AQP4, aquaporin 4; BM, basement membrane; EC, endothelial cell; IL-17, interleukin 17; PVS, perivascular space; sAPPβ, soluble peptide APPβ; and SMC, smooth muscle cell.

proteinopathy by disrupting Aβ and tau clearance. In a study using particle tracking velocimetry concurrent with measurements of arterial diameter, acute elevations in BP induced by intravenous infusion of AngII in mice altered arterial wall motion during the cardiac cycle, leading to reduced CSF flux in the PVS consequent to increased backflow.[150] This diminished CSF flow within the PVS could precipitate a similar decrease in glymphatic transport, a phenomenon recently demonstrated in the SHR model using dynamic contrast-enhanced MRI-aided quantification of the glymphatic transport of a contrast agent.[151] These perturbations are likely to diminish Aβ and tau removal. Indeed, TGN-020-mediated inhibition of AQP4 in astrocytic end feet,[149] which are crucial for glymphatic flow,[80] suppressed tau protein clearance in mice.[149] Considering recent observations that changes in vasomotion caused by neurovascular coupling or optogenetically induced vascular constriction-dilation facilitate CSF flow,[148,152] the neurovascular uncoupling observed in experimental and human hypertension[67,82,89,93] could compromise metabolite clearance. Lastly, RAGE, which is activated in hypertensive models,[153] modulates the entry of Aβ into the brain and influences β- and γ-secretase activity,[154] suggesting that hypertension could promote Aβ accumulation by enhancing Aβ influx[153] and β-amyloidogenesis through RAGE induction.[154]

Evidence for disruption of these pathways in human hypertension is limited. Elevated peripheral expression of extracellular RAGE binding protein was associated with increased risk of cognitive decline in the Rotterdam Study,[155] suggesting a role for RAGE in AD pathogenesis; however, this cross-sectional association was attenuated in a longitudinal setting,[155] indicating potential reverse causation. Human studies of SVD, in which the majority of participants were hypertensive, showed evidence of reduced glymphatic clearance,[156] but a specific role of elevated BP has not been established.

Collectively, these clinical and basic observations suggest that hypertension could contribute to AD pathology through induction of amyloidogenesis and, based mainly on animal studies, diminution of amyloid/tau clearance (Figure 4), although the degree to which hypertension affects these pathways in humans requires elucidation.

SUMMARY: HOW DOES HYPERTENSION PROMOTE COGNITIVE DETERIORATION?

Hypertension likely contributes to cognitive decline through a confluence of pathogenic mechanisms (Figure 5). First, vascular damages, inflammation, neurovascular dysfunction, and BBB disruption threaten the health of the cortical tissue and subcortical white matter. The resulting WMLs, microinfarcts, microbleeds, and disruption of metabolite clearance may contribute to network dysfunction, neuronal loss, and brain atrophy. Finally, by fostering Aβ and p-tau accumulation, hypertension could conceivably contribute to the overlap between vascular and AD pathology to accelerate the development of cognitive impairment.

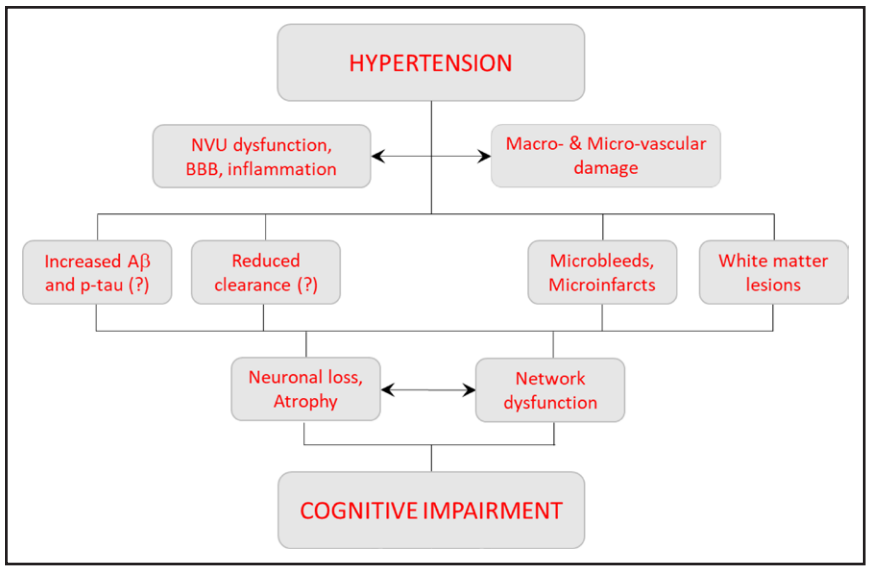

Figure 5. Hypertensive sequalae that underlie cognitive impairment. Hypertension promotes structural alterations to the cerebrovasculature concurrent with NVU functional deficits. The resultant microbleeds, microinfarcts, and local hypoxia-ischemia drive neuronal loss and degradation of white matter tracts (especially in thalamo-cortico circuits), leading to brain atrophy and network disruption. Additionally, hypertension may provoke β-amyloidogenesis (upregulated secretase activity) and disrupt clearance of toxic metabolites, giving rise to Alzheimer's-associated proteinopathies. Collectively, these events likely contribute to cognitive impairment. CBF indicates cerebral blood flow; NVU, neurovascular unit; and WML, white matter lesion.

THERAPEUTIC INTERVENTIONS

A recent postmortem investigation of samples taken from 4 separate birth cohorts (1905–1914, 1915–1919, 1920–1924, and 1925–1930) found that although neurodegenerative pathologies did not differ by birth year, dementia incidence decreased over time concurrently with atherosclerosis and arteriosclerosis.[157] The dramatic reduction in vascular pathology, possibly due to better control of vascular risk factors, including hypertension, could have contributed to the decrease in dementia incidence. Considering epidemiological associations of hypertension with dementia, elevated BP presents a particularly inviting modifiable target in the effort to diminish global dementia burden.

Role for Antihypertensive Therapy?

As previously discussed (see hypertension and cognitive decline: epidemiological evidence), the relationship between hypertension and cognitive decline is most pronounced when considered in mid life.[1–3] Thus, although randomized clinical trials would best evaluate the efficacy of antihypertensive therapy in dementia prophylaxis, the temporal characteristics of the hypertension-dementia relationship necessitate reliance on long-term observational studies.

Several large cohort longitudinal analyses indicate an association of antihypertensive treatment with lesser cognitive decline.[2,158,159] Consistent with the relationship of hypertension chronicity to dementia risk,[160] therapy duration appears important in prophylaxis: in the Rotterdam cohort, each additional year of antihypertensive treatment, before age 75, reduced dementia risk by 8%.[159]

Clinical trial data are comparatively conflicting, likely due to issues surrounding the age of treatment onset and duration of medication use. Indeed, the most recent update of the Cochrane Review found that pharmacological treatment of hypertension in patients without prior cerebrovascular disease provides only low certainty evidence for the prevention of dementia onset and cognitive deterioration,[11] with investigators citing insufficient study duration as a probable confound. In contrast, a recent meta-analysis of 12 major clinical trials, including the recently completed SBP Intervention Trial-Memory and Cognition in Decreased Hypertension (SPRINT-MIND) study, reported a significant association of BP control with decreased risk of dementia or cognitive impairment.[161]

Intriguingly, intensive BP-lowering regimens may offer increased benefit relative to standard therapy. Recent findings from secondary analyses of the SPRINT-MIND data set indicate diminished risk of cognitive decline,[10,95] WML development,[162] and probable dementia[9] in patients undergoing intensive blood-pressure-lowering (SBP <120 mm Hg). Intensive regimens, but not standard, were also found to ameliorate cognitive decline in patients with high BPV.[163] Overall, these findings are corroborated by a recent meta-analysis where late-mid-to-late-life BP correction dramatically mitigated dementia risk, with intensive lowering showing the most benefit.[164] Taking into account the demonstrated safety of BP-lowering interventions in the elderly,[165] aggressive BP control warrants further consideration as a means to delay dementia onset.

Comparative assessments of differing antihypertensive agents have yielded inconsistent results. Although some meta-analyses show no heterogeneity of antihypertensive class on the risk of incident dementia,[12] an emerging body of evidence seemingly supports improved outcomes for drugs that preserve AngII synthesis (such as ARBs) over those that inhibit it (ACE [angiotensin-converting enzyme] inhibitors).[13] The BBB permeability

of drugs may also be consequential, with recent reports suggesting BBB-permeable ARBs[14] and β-blockers[166] are superior to their impermeable counterparts. Finally, the recent development of a selective aldosterone synthase inhibitor[167] and powerful angiotensinogen silencing antisense oligos[168] could allow for BP control in treatment-resistant hypertensive patients.

CONCLUSIONS

The data presented herein show that hypertension remains among the most insidious factors influencing cognition over the lifespan, largely due to impacts on cerebrovascular structure and function which threaten the health of the brain.[16] Despite advances in the field, numerous questions remain regarding the temporality of hypertension-induced cognitive decline, the underlying mechanisms, and potential interventions.

- Because the best clinical evidence for preserving cognition in hypertension currently supports BP control, it is important to consider whether certain drug classes are more efficacious than others. Although many studies fail to show heterogeneity among the antihypertensive classes,[12] AngII-preserving drugs[13] and BBB-crossing antihypertensives[14] and β-blockers,[166] as discussed in the previous section, warrant further exploration.
- Another important question is whether intensive BP control provides greater cognitive benefit than standard treatment. Results from SPRINT-MIND secondary analyses suggest this to be the case,[10] particularly in those with increased BPV.[163] Although this more aggressive approach does not compromise cerebral perfusion,[165] the risk/reward ratio of intensive treatment requires further validation (will adverse effects emerge as treatment length increases, or in the elderly?), and it remains to be determined whether aggressive control in mid-life, when the hypertension-cognitive decline relationship is strongest,[1–3] will still provide greater benefit.
- Does combating cognitive deterioration by controlling BP also reduce AD pathology? Since the neurohumoral dysfunction underlying hypertension may promote Aβ and p-tau accumulation, it would be of interest to assess if antihypertensive medications reduce AD pathology independently of effects on BP, as suggested by animal studies.[145] If so, antihypertensives could be combined with Aβ immunotherapy, which has recently been approved by the FDA.
- Considering preclinical evidence that the cerebrovascular sequelae of hypertension are not entirely ascribable to elevated BP,[82,89,93,102] further elucidation of the mechanistic underpinnings of neurovascular and cognitive impairment in hypertension are needed. Are immune cells a major driving force? In addition to the growing body of experimental evidence connecting PVMs to hypertensive pathology,[82,93,102] the recently unveiled contributions of meningeal T cells to neurovascular dysfunction in a model of salt-sensitive hypertension[93] links meningeal immunity to hypertension-induced cognitive impairment.
- What about pericytes, which may be involved in BBB regulation and cerebral perfusion[169]? Reduced capillary pericyte coverage is observed alongside BBB disruption in slow-pressor AngII hypertension,[170] and mouse models of pericyte deficiency exhibit impairment of the BBB[171] and CBF regulation.[172] However, the precise contributions of pericyte alteration to the neurovascular and cognitive dysfunction in hypertension remain to be determined and would be an area of interest for future studies.
- The events linking vascular dysfunction with disruption of neuronal function and cognitive impairment have yet to be defined. How does derangement of specific vascular cells by hypertension contribute to neuronal dysfunction? scRNA-seq-based studies could help unveil the hypertension-induced molecular changes that occur within these cells, potentially leading to new diagnostic insights. Is a mismatch between energy demand and blood supply consequent to hemodynamic insufficiency enough to drive cognitive decline? Or are events such as loss of endothelial trophic support and diminished clearance of metabolites of equal (or greater) importance? Answering these questions would provide new leads and, potentially, new therapeutic targets.
- How do aging and sex modulate these relationships? At present, most animal studies have been performed in young males.[88] Given that age and sex modulate the development and expression of hypertension in the AngII, SHR, Dahl salt-sensitive, and DOCA-salt models,[173] future research into the influence of these factors on neurovascular and cognitive dysfunction in hypertension would be illuminating and relevant to the human disease, which affects mainly aged individuals of both sexes.

These are a few of the outstanding questions that remain to be addressed. Rapid advances in neurovascular biology, an increased appreciation for the role of the neurovasculome in health and disease, and powerful new methodological approaches will expand our knowledge of the impacts of vascular sequela on cognitive function in hypertension. In closing, synchrony of biomarker and clinical-pathological studies with basic science mechanistic investigations will be essential for the advancement of new diagnostic tools and treatment interventions in the effort to preserve cognitive health over the lifespan.

ARTICLE INFORMATION

Affiliation

Feil Family Brain and Mind Research Institute, Weill Cornell Medicine, New York, NY.

Acknowledgments

The authors gratefully thank the Feil Family Foundation for the support. Figures were prepared using BioRender.com.

Sources of Funding

The study was supported by NIH grants NS126467, NS095441, NS/HL37853, and NS128947.

Disclosures

C. Iadecola serves on the scientific advisory board of Broadview Ventures. The other author reports no conflicts.

REFERENCES

1. Swan GE, DeCarli C, Miller BL, Reed T, Wolf PA, Jack LM, Carmelli D. Association of midlife blood pressure to late-life cognitive decline and brain morphology. *Neurology*. 1998;51:986–993. doi: 10.1212/wnl.51.4.986
2. Gottesman RF, Schneider AL, Albert M, Alonso A, Bandeen-Roche K, Coker L, Coresh J, Knopman D, Power MC, Rawlings A, et al. Midlife hypertension and 20-year cognitive change: the atherosclerosis risk in communities neurocognitive study. *JAMA Neurol*. 2014;71:1218–1227. doi: 10.1001/jamaneurol.2014.1646
3. Gottesman RF, Albert MS, Alonso A, Coker LH, Coresh J, Davis SM, Deal JA, McKhann GM, Mosley TH, Sharrett AR, et al. Associations between midlife vascular risk factors and 25-year incident dementia in the atherosclerosis risk in communities (ARIC) cohort. *JAMA Neurol*. 2017;74:1246–1254. doi: 10.1001/jamaneurol.2017.1658
4. Kety SS, Schmidt CF. The nitrous oxide method for the quantitative determination of cerebral blood flow in man: theory, procedure, and normal values. *J Clin Invest*. 1948;27:476–483. doi: 10.1172/JCI101994
5. Leopold IH, Kety SS. Correlation of the cerebrovascular resistance and the grade of hypertensive retinal findings. *Am J Ophthalmol*. 1949;32:365–368. doi: 10.1016/0002-9394(49)91928-5
6. Spieth W. Cardiovascular health status, age, and psychological performance. *J Gerontol*. 1964;19:277–284. doi: 10.1093/geronj/19.3.277
7. Wilkie F, Eisdorfer C. Intelligence and blood pressure in the aged. *Science (New York, NY)*. 1971;172:959–962. doi: 10.1126/science.172.3986.959
8. Iadecola C, Duering M, Hachinski V, Joutel A, Pendlebury ST, Schneider JA, Dichgans M. Vascular cognitive impairment and dementia: JACC scientific expert panel. *J Am Coll Cardiol*. 2019;73:3326–3344. doi: 10.1016/j.jacc.2019.04.034
9. Williamson JD, Pajewski NM, Auchus AP, Bryan RN, Chelune G, Cheung AK, Cleveland ML, Coker LH, Crowe MG, Cushman WC, et al; SPRINT MIND Investigators for the SPRINT Research Group. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. *JAMA*. 2019;321:553–561. doi: 10.1001/jama.2018.21442
10. Elahi FM, Alladi S, Black SE, Claassen JAHR, DeCarli C, Hughes TM, Moonen J, Pajewski NM, Price BR, Satizabal C, et al. Clinical trials in vascular cognitive impairment following SPRINT-MIND: an international perspective. *Cell Rep Med*. 2023;4:101089. doi: 10.1016/j.xcrm.2023.101089
11. Cunningham EL, Todd SA, Passmore P, Bullock R, McGuinness B. Pharmacological treatment of hypertension in people without prior cerebrovascular disease for the prevention of cognitive impairment and dementia. *Cochrane Database Syst Rev*. 2021;5:CD004034. doi: 10.1002/14651858.CD004034.pub4
12. Ding J, Davis-Plourde KL, Sedaghat S, Tully PJ, Wang W, Phillips C, Pase MP, Himali JJ, Gwen Windham B, Griswold M, 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. doi: 10.1016/S1474-4422(19)30393-X
13. Marcum ZA, Cohen JB, Zhang C, Derington CG, Greene TH, Ghazi L, Herrick JS, King JB, Cheung AK, Bryan N, et al; Systolic Blood Pressure Intervention Trial (SPRINT) Research Group. Association of antihypertensives that stimulate vs inhibit types 2 and 4 angiotensin II receptors with cognitive impairment. *JAMA Netw Open*. 2022;5:e2145319. doi: 10.1001/jamanetworkopen.2021.45319
14. Ho JK, Moriarty F, Manly JJ, Larson EB, Evans DA, Rajan KB, Hudak EM, Hassan L, Liu E, Sato N, et al. Blood-brain barrier crossing renin-angiotensin drugs and cognition in the elderly: a meta-analysis. *Hypertension*. 2021;78:629–643. doi: 10.1161/HYPERTENSIONAHA.121.17049
15. Franklin SS, Gustin W, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation*. 1997;96:308–315. doi: 10.1161/01.cir.96.1.308
16. Iadecola C, Gottesman RF. Neurovascular and Cognitive Dysfunction in Hypertension. *Circ Res*. 2019;124:1025–1044. doi: 10.1161/CIRCRESAHA.118.313260
17. Ungvari Z, Toth P, Tarantini S, Prodan CI, Sorond F, Merkely B, Csiszar A. Hypertension-induced cognitive impairment: from pathophysiology to public health. *Nat Rev Nephrol*. 2021;17:639–654. doi: 10.1038/s41581-021-00430-6
18. Glynn RJ, Beckett LA, Hebert LE, Morris MC, Scherr PA, Evans DA. Current and remote blood pressure and cognitive decline. *JAMA*. 1999;281:438–445. doi: 10.1001/jama.281.5.438
19. Stewart R, Xue QL, Masaki K, Petrovitch H, Ross GW, White LR, Launer LJ. Change in blood pressure and incident dementia: a 32-year prospective study. *Hypertension*. 2009;54:233–240. doi: 10.1161/HYPERTENSIONAHA.109.128744
20. Power MC, Schneider AL, Wruck L, Griswold M, Coker LH, Alonso A, Jack CR, Knopman D, Mosley TH, Gottesman RF. Life-course blood pressure in relation to brain volumes. *Alzheimers Dement*. 2016;12:890–899. doi: 10.1016/j.jalz.2016.03.012
21. Burke WJ, Coronado PG, Schmitt CA, Gillespie KM, Chung HD. Blood pressure regulation in Alzheimer's disease. *J Auton Nerv Syst*. 1994;48:65–71. doi: 10.1016/0165-1838(94)90160-0
22. Rosei EA, Chiarini G, Rizzoni D. How important is blood pressure variability? *Eur Heart J Suppl*. 2020;22:E1–E6. doi: 10.1093/eurheartj/suaa061
23. Asmuje NF, Mat S, Myint PK, Tan MP. Blood pressure variability and cognitive function: a scoping review. *Curr Hypertens Rep*. 2022;24:375–383. doi: 10.1007/s11906-022-01200-w
24. de Heus RAA, Tzourio C, Lee EJL, Opozda M, Vincent AD, Anstey KJ, Hofman A, Kario K, Lattanzi S, Launer LJ, et al; VARIABLE BRAIN Consortium. Association between blood pressure variability with dementia and cognitive impairment: a systematic review and meta-analysis. *Hypertension*. 2021;78:1478–1489. doi: 10.1161/HYPERTENSIONAHA.121.17797
25. Iadecola C. The neurovascular unit coming of age: a journey through neurovascular coupling in health and disease. *Neuron*. 2017;96:17–42. doi: 10.1016/j.neuron.2017.07.030
26. Iadecola C, Smith EE, Anrather J, Gu C, Mishra A, Misra S, Perez-Pinzon MA, Shih AY, Sorond FA, van Veluw SJ, et al; American Heart Association Stroke Council Council on Arteriosclerosis Thrombosis and Vascular Biology Council on Cardiovascular Radiology and Intervention Council on Hypertension Council on Lifestyle and Cardiometabolic Health. 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. doi: 10.1161/STR.0000000000000431
27. Kaess BM, Rong J, Larson MG, Hamburg NM, Vita JA, Levy D, Benjamin EJ, Vasan RS, Mitchell GF. Aortic stiffness, blood pressure progression, and incident hypertension. *JAMA*. 2012;308:875–881. doi: 10.1001/2012.jama.10503
28. O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. *Hypertension*. 2005;46:200–204. doi: 10.1161/01.HYP.0000168052.00426.65
29. 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–H1614. doi: 10.1152/ajpheart.00490.2012
30. Iulita MF, Noriega de la Colina A, Girouard H. Arterial stiffness, cognitive impairment and dementia: confounding factor or real risk? *J Neurochem*. 2018;144:527–548. doi: 10.1111/jnc.14235
31. Norlander AE, Madhur MS, Harrison DG. The immunology of hypertension. *J Exp Med*. 2018;215:21–33. doi: 10.1084/jem.20171773
32. Ogola BO, Zimmerman MA, Clark GL, Abshire CM, Gentry KM, Miller KS, Lindsey SH. New insights into arterial stiffening: does sex matter? *Am J Physiol Heart Circ Physiol*. 2018;315:H1073–H1087. doi: 10.1152/ajpheart.00132.2018
33. Hollander W, Prusty S, Kemper T, Rosene DL, Moss MB. The effects of hypertension on cerebral atherosclerosis in the cynomolgus monkey. *Stroke*. 1993;24:1218–26; discussion 1226. doi: 10.1161/01.str.24.8.1218
34. Qureshi AI, Caplan LR. Intracranial atherosclerosis. *Lancet*. 2014;383:984–998. doi: 10.1016/S0140-6736(13)61088-0

35. Hui Chen L, Spagnolo-Allende A, Yang D, Qiao Y, Gutierrez J. Epidemiology, pathophysiology, and imaging of atherosclerotic intracranial disease. Review-article. *Stroke*. 2024;55:311–323. doi: 10.1161/STROKEAHA.123.043630
36. Agmon Y, Khandheria BK, Meissner I, Schwartz GL, Petterson TM, O'Fallon WM, Gentile F, Whisnant JP, Wiebers DO, Seward JB. Independent association of high blood pressure and aortic atherosclerosis: a population-based study. *Circulation*. 2000;102:2087–2093. doi: 10.1161/01.cir.102.17.2087
37. Weiss D, Sorescu D, Taylor WR. Angiotensin II and atherosclerosis. *Am J Cardiol*. 2001;87:25C–32C. doi: 10.1016/s0002-9149(01)01539-9
38. Jefferson AL, Cambronero FE, Liu D, Moore EE, Neal JE, Terry JG, Nair S, Pechman KR, Rane S, Davis LT, et al. Higher aortic stiffness is related to lower cerebral blood flow and preserved cerebrovascular reactivity in older adults. *Circulation*. 2018;138:1951–1962. doi: 10.1161/CIRCULATIONAHA.118.032410
39. DuBose LE, Boles Ponto LL, Moser DJ, Harlynn E, Reierson L, Pierce GL. Higher aortic stiffness is associated with lower global cerebrovascular reserve among older humans. *Hypertension*. 2018;72:476–482. doi: 10.1161/HYPERTENSIONAHA.118.11143
40. Gupta A, Chazen JL, Hartman M, Delgado D, Anumula N, Shao H, Mazumdar M, Segal AZ, Kamel H, Leifer D, et al. Cerebrovascular reserve and stroke risk in patients with carotid stenosis or occlusion: a systematic review and meta-analysis. *Stroke*. 2012;43:2884–2891. doi: 10.1161/STROKEAHA.112.663716
41. van Sloten TT, Protogerou AD, Henry RM, Schram MT, Launer LJ, Stehouwer CD. Association between arterial stiffness, cerebral small vessel disease and cognitive impairment: A systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2015;53:121–130. doi: 10.1016/j.neubiorev.2015.03.011
42. Blevins BL, Vinters HV, Love S, Wilcock DM, Grinberg LT, Schneider JA, Kalaria RN, Katsumata Y, Gold BT, Wang DJJ, et al. Brain arteriolosclerosis. *Acta Neuropathol*. 2021;141:1–24. doi: 10.1007/s00401-020-02235-6
43. Hainsworth AH, Markus HS, Schneider JA. Cerebral small vessel disease, hypertension, and vascular contributions to cognitive impairment and dementia. *Hypertension*. 2024;81:75–86. doi: 10.1161/HYPERTENSIONAHA.123.19943
44. Lammie GA. Hypertensive cerebral small vessel disease and stroke. *Brain Pathol*. 2002;12:358–370. doi: 10.1111/j.1750-3639.2002.tb00450.x
45. Blanco PJ, Müller LO, Spence JD. Blood pressure gradients in cerebral arteries: a clue to pathogenesis of cerebral small vessel disease. *Stroke Vasc Neurol*. 2017;2:108–117. doi: 10.1136/svn-2017-000087
46. Shih AY, Blinder P, Tsai PS, Friedman B, Stanley G, Lyden PD, Kleinfeld D. The smallest stroke: occlusion of one penetrating vessel leads to infarction and a cognitive deficit. *Nat Neurosci*. 2013;16:55–63. doi: 10.1038/nn.3278
47. Brown WR, Moody DM, Thore CR, Challa VR, Anstrom JA. Vascular dementia in leukoaraiosis may be a consequence of capillary loss not only in the lesions, but in normal-appearing white matter and cortex as well. *J Neurol Sci*. 2007;257:62–66. doi: 10.1016/j.jns.2007.01.015
48. Ter Telgte A, van Leijsen EMC, Wiegertjes K, Klijn CJM, Tuladhar AM, de Leeuw FE. Cerebral small vessel disease: from a focal to a global perspective. *Nat Rev Neurol*. 2018;14:387–398. doi: 10.1038/s41582-018-0014-y
49. Keith J, Gao FQ, Noor R, Kiss A, Balasubramaniam G, Au K, Rogaeva E, Masellis M, Black SE. Collagenosis of the deep medullary veins: an under-recognized pathologic correlate of white matter hyperintensities and periventricular infarction? *J Neuropathol Exp Neurol*. 2017;76:299–312. doi: 10.1093/jnen/nlx009
50. Wardlaw JM, Benveniste H, Nedergaard M, Zlokovic BV, Mestre H, Lee H, Doubal FN, Brown R, Ramirez J, MacIntosh BJ, et al; Colleagues from the Fondation Leducq Transatlantic Network of Excellence on the Role of the Perivascular Space in Cerebral Small Vessel Disease. Perivascular spaces in the brain: anatomy, physiology and pathology. *Nat Rev Neurol*. 2020;16:137–153. doi: 10.1038/s41582-020-0312-z
51. Tully PJ, Yano Y, Launer LJ, Kario K, Nagai M, Mooijaart SP, Claassen JAHR, Lattanzi S, Vincent AD, Tzourio C; Variability in Blood Pressure and Brain Health Consortium. Association between blood pressure variability and cerebral small-vessel disease: a systematic review and meta-analysis. *J Am Heart Assoc*. 2020;9:e013841. doi: 10.1161/JAHA.119.013841
52. Ma Y, Blacker D, Viswanathan A, van Veluw SJ, Bos D, Vernooij MW, Hyman BT, Tzourio C, Das S, Hofman A. Visit-to-visit blood pressure variability, neuropathology, and cognitive decline. *Neurology*. 2021;96:e2812–e2823. doi: 10.1212/WNL.0000000000012065
53. Claassen JAHR, 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. doi: 10.1152/physrev.00022.2020
54. Ashby JW, Mack JJ. Endothelial control of cerebral blood flow. *Am J Pathol*. 2021;191:1906–1916. doi: 10.1016/j.ajpath.2021.02.023
55. Lassen NA. Cerebral blood flow and oxygen consumption in man. *Physiol Rev*. 1959;39:183–238. doi: 10.1152/physrev.1959.39.2.183
56. Aaslid R, Lindegaard KF, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. *Stroke*. 1989;20:45–52. doi: 10.1161/01.str.20.1.45
57. Newell DW, Aaslid R, Lam A, Mayberg TS, Winn HR. Comparison of flow and velocity during dynamic autoregulation testing in humans. *Stroke*. 1994;25:793–797. doi: 10.1161/01.str.25.4.793
58. Mederos y Schnitzler M, Storch U, Meibers S, Nurwakagari P, Breit A, Essin K, Gollasch M, Gudermann T. Gq-coupled receptors as mechanosensors mediating myogenic vasoconstriction. *EMBO J*. 2008;27:3092–3103. doi: 10.1038/emboj.2008.233
59. Jarajapu YP, Knot HJ. Relative contribution of Rho kinase and protein kinase C to myogenic tone in rat cerebral arteries in hypertension. *Am J Physiol Heart Circ Physiol*. 2005;289:1917–1922. doi: 10.1152/ajpheart.01012.2004
60. Knot HJ, Nelson MT. Regulation of arterial diameter and wall [Ca^{2+}] in cerebral arteries of rat by membrane potential and intravascular pressure. *J Physiol*. 1998;508 (Pt 1):199–209. doi: 10.1111/j.1469-7793.1998.199br.x
61. Immink RV, van den Born BJ, van Montfrans GA, Koopmans RP, Karemaker JM, van Lieshout JJ. Impaired cerebral autoregulation in patients with malignant hypertension. *Circulation*. 2004;110:2241–2245. doi: 10.1161/01.CIR.0000144472.08647.40
62. Longden TA, Dabertrand F, Koide M, Gonzales AL, Tykocki NR, Brayden JE, Hill-Eubanks D, Nelson MT. Capillary K(+)-sensing initiates retrograde hyperpolarization to increase local cerebral blood flow. *Nat Neurosci*. 2017;20:717–726. doi: 10.1038/nn.4533
63. Iadecola C, Yang G, Ebner TJ, Chen G. Local and propagated vascular responses evoked by focal synaptic activity in cerebellar cortex. *J Neurophysiol*. 1997;78:651–659. doi: 10.1152/jn.1997.78.2.651
64. Chen BR, Kozberg MG, Bouchard MB, Shaik MA, Hillman EM. A critical role for the vascular endothelium in functional neurovascular coupling in the brain. *J Am Heart Assoc*. 2014;3:e000787. doi: 10.1161/JAHA.114.000787
65. Jennings JR, Muldoon MF, Ryan C, Price JC, Greer P, Sutton-Tyrrell K, van der Veen FM, Meltzer CC. Reduced cerebral blood flow response and compensation among patients with untreated hypertension. *Neurology*. 2005;64:1358–1365. doi: 10.1212/01.WNL.0000158283.28251.3C
66. Delles C, Michelson G, Harazny J, Oehmer S, Hilgers KF, Schmieder RE. Impaired endothelial function of the retinal vasculature in hypertensive patients. *Stroke*. 2004;35:1289–1293. doi: 10.1161/01.STR.0000126597.11534.3b
67. Junejo RT, Braz ID, Lucas SJ, van Lieshout JJ, Phillips AA, Lip GY, Fisher JP. Neurovascular coupling and cerebral autoregulation in atrial fibrillation. *J Cereb Blood Flow Metab*. 2020;40:1647–1657. doi: 10.1177/0271678X19870770
68. Toda N, Ayajiki K, Okamura T. Cerebral blood flow regulation by nitric oxide: recent advances. *Pharmacol Rev*. 2009;61:62–97. doi: 10.1124/pr.108.000547
69. Kraehling JR, Sessa WC. Contemporary approaches to modulating the nitric oxide-cGMP pathway in cardiovascular disease. *Circ Res*. 2017;120:1174–1182. doi: 10.1161/CIRCRESAHA.117.303776
70. Sweeney MD, Zhao Z, Montagne A, Nelson AR, Zlokovic BV. Blood-brain barrier: from physiology to disease and back. *Physiol Rev*. 2019;99:21–78. doi: 10.1152/physrev.00050.2017
71. Daiber A, Steven S, Weber A, Shuvaev VV, Muzykantov VR, Laher I, Li H, Lamas S, Münzel T. Targeting vascular (endothelial) dysfunction. *Br J Pharmacol*. 2017;174:1591–1619. doi: 10.1111/bph.13517
72. Bagi Z, Brandner DD, Le P, McNeal DW, Gong X, Dou H, Fulton DJ, Beller A, Ngyuen T, Larson EB, et al. Vasodilator dysfunction and oligodendrocyte dysmaturation in aging white matter. *Ann Neurol*. 2018;83:142–152. doi: 10.1002/ana.25129
73. Nezu T, Hosomi N, Aoki S, Kubo S, Araki M, Mukai T, Takahashi T, Maruyama H, Higashi Y, Matsumoto M. Endothelial dysfunction is associated with the severity of cerebral small vessel disease. *Hypertens Res*. 2015;38:291–297. doi: 10.1038/hr.2015.4
74. Hoth KF, Tate DF, Poppas A, Forman DE, Gunstad J, Moser DJ, Paul RH, Jefferson AL, Haley AP, Cohen RA. Endothelial function and white matter hyperintensities in older adults with cardiovascular disease. *Stroke*. 2007;38:308–312. doi: 10.1161/01.STR.0000254517.04275.3f
75. da Silva PHR, de Leeuw FE, Zotin MCZ, Neto OMP, Leoni RF, Tuladhar AM. Cortical thickness and brain connectivity mediate the relation between white matter hyperintensity and information processing speed in cerebral small vessel disease. *Brain Topogr*. 2023;36:613–630. doi: 10.1007/s10548-023-00973-w
76. Akoudad S, Wolters FJ, Viswanathan A, de Bruijn RF, van der Lugt A, Hofman A, Koudstaal PJ, Ikram MA, Vernooij MW. Association of cerebral microbleeds with cognitive decline and dementia. *JAMA Neurol*. 2016;73:934–943. doi: 10.1001/jamaneurol.2016.1017

77. Muñoz Maniega S, Chappell FM, Valdés Hernández MC, Armitage PA, Makin SD, Heye AK, Thrippleton MJ, Sakka E, Shuler K, Dennis MS, et al. Integrity of normal-appearing white matter: influence of age, visible lesion burden and hypertension in patients with small-vessel disease. *J Cereb Blood Flow Metab*. 2017;37:644–656. doi: 10.1177/0271678X16635657
78. Tarasoff-Conway JM, Carare RO, Osorio RS, Glodzik L, Butler T, Fieremans E, Axel L, Rusinek H, Nicholson C, Zlokovic BV, et al. Clearance systems in the brain-implications for Alzheimer disease. *Nat Rev Neurol*. 2015;11:457–470. doi: 10.1038/nrneurol.2015.119
79. Morris AW, Sharp MM, Albargothy NJ, Fernandes R, Hawkes CA, Verma A, Weller RO, Carare RO. Vascular basement membranes as pathways for the passage of fluid into and out of the brain. *Acta Neuropathol*. 2016;131:725–736. doi: 10.1007/s00401-016-1555-z
80. Rasmussen MK, Mestre H, Nedergaard M. Fluid transport in the brain. *Physiol Rev*. 2022;102:1025–1151. doi: 10.1152/physrev.00031.2020
81. Amann L, Masuda T, Prinz M. Mechanisms of myeloid cell entry to the healthy and diseased central nervous system. *Nat Immunol*. 2023;24:393–407. doi: 10.1038/s41590-022-01415-8
82. Faraco G, Sugiyama Y, Lane D, Garcia-Bonilla L, Chang H, Santisteban MM, Racchumi G, Murphy M, Van Rooijen N, Anrather J, et al. Perivascular macrophages mediate the neurovascular and cognitive dysfunction associated with hypertension. *J Clin Invest*. 2016;126:4674–4689. doi: 10.1172/JCI86950
83. Pires PW, Girgla SS, McClain JL, Kaminski NE, van Rooijen N, Dorrance AM. Improvement in middle cerebral artery structure and endothelial function in stroke-prone spontaneously hypertensive rats after macrophage depletion. *Microcirculation*. 2013;20:650–661. doi: 10.1111/micc.12064
84. Zhu YC, Tzourio C, Soumaré A, Mazoyer B, Dufouil C, Chabriat H. Severity of dilated Virchow-Robin spaces is associated with age, blood pressure, and MRI markers of small vessel disease: a population-based study. *Stroke*. 2010;41:2483–2490. doi: 10.1161/STROKEAHA.110.591586
85. van den Kerkhof M, van der Thiel MM, van Oostenbrugge RJ, Postma AA, Kroon AA, Backes WH, Jansen JF. Impaired damping of cerebral blood flow velocity pulsatility is associated with the number of perivascular spaces as measured with 7T MRI. *J Cereb Blood Flow Metab*. 2023;43:937–946. doi: 10.1177/0271678X231153374
86. van den Kerkhof M, van der Thiel MM, Postma AA, van Oostenbrugge RJ, Kroon AA, Jansen JFA, Backes WH. Hypertension correlates with stronger blood flow pulsatility in small perforating cerebral arteries assessed with 7 tesla magnetic resonance imaging. *Hypertension*. 2023;80:802–810. doi: 10.1161/HYPERTENSIONAHA.122.19866
87. Zhang M, Tang J, Xia D, Xue Y, Ren X, Huang Q, Shi L, Tang W, Fu J. Evaluation of glymphatic-meningeal lymphatic system with intravenous gadolinium-based contrast-enhancement in cerebral small-vessel disease. *Eur Radiol*. 2023;33: 6096–6106. doi: 10.1007/s00330-023-09796-6
88. Lerman LO, Kurtz TW, Touyz RM, Ellison DH, Chade AR, Crowley SD, Mattson DL, Mullins JJ, Osborn J, Eirin A, et al. Animal models of hypertension: a scientific statement from the American Heart Association. *Hypertension*. 2019;73:e87–e120. doi: 10.1161/HYP.0000000000000090
89. Kazama K, Anrather J, Zhou P, Girouard H, Frys K, Milner TA, Iadecola C. Angiotensin II impairs neurovascular coupling in neocortex through NADPH oxidase-derived radicals. *Circ Res*. 2004;95:1019–1026. doi: 10.1161/01.RES.0000148637.85595.c5
90. Capone C, Faraco G, Peterson JR, Coleman C, Anrather J, Milner TA, Pickel VM, Davisson RL, Iadecola C. Central cardiovascular circuits contribute to the neurovascular dysfunction in angiotensin II hypertension. *J Neurosci*. 2012;32:4878–4886. doi: 10.1523/JNEUROSCI.6262-11.2012
91. Capone C, Faraco G, Park L, Cao X, Davisson RL, Iadecola C. The cerebrovascular dysfunction induced by slow pressor doses of angiotensin II precedes the development of hypertension. *Am J Physiol Heart Circ Physiol*. 2011;300:H397–H407. doi: 10.1152/ajpheart.00679.2010
92. Calcinaghi N, Wyss MT, Jolivet R, Singh A, Keller AL, Winnik S, Fritschy J-M, Buck A, Matter CM, Weber B. Multimodal imaging in rats reveals impaired neurovascular coupling in sustained hypertension. *Stroke*. 2013;44:1957–1964. doi: 10.1161/STROKEAHA.111.000185
93. Santisteban MM, Schaeffer S, Anfray A, Faraco G, Brea D, Wang G, Sobanko MJ, Sciortino R, Racchumi G, Waisman A, et al. Meningeal interleukin-17-producing T cells mediate cognitive impairment in a mouse model of salt-sensitive hypertension. *Nat Neurosci*. 2024;27:63–77. doi: 10.1038/s41593-023-01497-z
94. Gorelick PB, Whelton PK, Sorond F, Carey RM. Blood pressure management in stroke. *Hypertension*. 2020;76:1688–1695. doi: 10.1161/HYPERTENSIONAHA.120.14653
95. Ghazi L, Shen J, Ying J, Derington CG, Cohen JB, Marcum ZA, Herrick JS, King JB, Cheung AK, Williamson JD, et al. Identifying patients for intensive blood pressure treatment based on cognitive benefit: a secondary analysis of the SPRINT randomized clinical trial. *JAMA Netw Open*. 2023;6:e2314443. doi: 10.1001/jamanetworkopen.2023.14443
96. Youwakim J, Vallerand D, Girouard H. Neurovascular coupling in hypertension is impaired by IL-17A through oxidative stress. *Int J Mol Sci*. 2023;24:3959. doi: 10.3390/ijms24043959
97. Paravicini TM, Touyz RM. NADPH oxidases, reactive oxygen species, and hypertension: clinical implications and therapeutic possibilities. *Diabetes Care*. 2008;31:S170–S180. doi: 10.2337/dc08-s247
98. Dröge W. Free radicals in the physiological control of cell function. *Physiol Rev*. 2002;82:47–95. doi: 10.1152/physrev.00018.2001
99. Girouard H, Park L, Anrather J, Zhou P, Iadecola C. Cerebrovascular nitrosative stress mediates neurovascular and endothelial dysfunction induced by angiotensin II. *Arterioscler Thromb Vasc Biol*. 2007;27:303–309. doi: 10.1161/01.ATV.0000253885.41509.25
100. Faraco G, Park L, Anrather J, Iadecola C. Brain perivascular macrophages: characterization and functional roles in health and disease. *J Mol Med*. 2017;95:1143–1152. doi: 10.1007/s00109-017-1573-x
101. Van Hove H, Martens L, Scheyltjens I, De Vlaminck K, Pombo Antunes AR, De Prijck S, Vandamme N, De Schepper S, Van Isterdael G, Scott CL, et al. A single-cell atlas of mouse brain macrophages reveals unique transcriptional identities shaped by ontogeny and tissue environment. *Nat Neurosci*. 2019;22:1021–1035. doi: 10.1038/s41593-019-0393-4
102. Santisteban MM, Ahn SJ, Lane D, Faraco G, Garcia-Bonilla L, Racchumi G, Poon C, Schaeffer S, Segarra SG, Körbelin J, et al. Endothelium-macrophage crosstalk mediates blood-brain barrier dysfunction in hypertension. *Hypertension*. 2020;76:795–807. doi: 10.1161/HYPERTENSIONAHA.120.15581
103. Ben-Zvi A, Lacoste B, Kur E, Andreone BJ, Mayshar Y, Yan H, Gu C. Mfsd2a is critical for the formation and function of the blood-brain barrier. *Nature*. 2014;509:507–511. doi: 10.1038/nature13324
104. Kerkhofs D, van Hagen BT, Milanova IV, Schell KJ, van Essen H, Wijnands E, Goossens P, Blankesteijn WM, Unger T, Prickaerts J, et al. Pharmacological depletion of microglia and perivascular macrophages prevents vascular cognitive impairment in Ang II-induced hypertension. *Theranostics*. 2020;10:9512–9527. doi: 10.7150/thno.44394
105. Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 Cells. *Annu Rev Immunol*. 2009;27:485–517. doi: 10.1146/annurev.immunol.021908.132710
106. Guzik TJ, Hoch NE, Brown KA, McCann LA, Rahman A, Dikalov S, Goronzy J, Weyand C, Harrison DG. Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. *J Exp Med*. 2007;204:2449–2460. doi: 10.1084/jem.20070657
107. Goldstein FC, Hajjar IM, Dunn CB, Levey AI, Wharton W. The relationship between cognitive functioning and the JNC-8 guidelines for hypertension in older adults. *J Gerontol A Biol Sci Med Sci*. 2017;72:121–126. doi: 10.1093/gerona/glw181
108. Reed BR, Mungas DM, Kramer JH, Ellis W, Vinters HV, Zarow C, Jagust WJ, Chui HC. Profiles of neuropsychological impairment in autopsy-defined Alzheimer's disease and cerebrovascular disease. *Brain*. 2007;130:731–739. doi: 10.1093/brain/awl385
109. van Veluw SJ, Shih AY, Smith EE, Chen C, Schneider JA, Wardlaw JM, Greenberg SM, Biessels GJ. Detection, risk factors, and functional consequences of cerebral microinfarcts. *Lancet Neurol*. 2017;16:730–740. doi: 10.1016/S1474-4422(17)30196-5
110. Biesbroek JM, Weaver NA, Biessels GJ. Lesion location and cognitive impact of cerebral small vessel disease. *Clin Sci*. 2017;131:715–728. doi: 10.1042/CS20160452
111. Martinez-Ramirez S, Greenberg SM, Viswanathan A. Cerebral microbleeds: overview and implications in cognitive impairment. *Alzheimer's Res Ther*. 2014;6:33. doi: 10.1186/alzrt263
112. Habes M, Erus G, Toledo JB, Zhang T, Bryan N, Launer LJ, Rosseel Y, Janowitz D, Doshi J, Van der Auwera S, et al. White matter hyperintensities and imaging patterns of brain ageing in the general population. *Brain*. 2016;139:1164–1179. doi: 10.1093/brain/aww008
113. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. *Lancet Neurol*. 2019;18:684–696. doi: 10.1016/S1474-4422(19)30079-1
114. Joutel A, Chabriat H. Pathogenesis of white matter changes in cerebral small vessel diseases: beyond vessel-intrinsic mechanisms. *Clin Sci*. 2017;131:635–651. doi: 10.1042/CS20160380
115. Jacob MA, Cai M, van de Donk V, Bergkamp M, Marques J, Norris DG, Kessels RPC, Claassen JAHR, Duering M, Tuladhar AM, et al. Cerebral small vessel disease progression and the risk of dementia: a

14-year follow-up study. *Am J Psychiatry*. 2023;180:508–518. doi: 10.1176/appi.ajp.20220380
116. Cai M, Jacob MA, van Loenen MR, Bergkamp M, Marques J, Norris DG, Duering M, Tuladhar AM, de Leeuw F-E. Determinants and temporal dynamics of cerebral small vessel disease: 14-year follow-up. *Stroke*. 2022;53:2789–2798. doi: 10.1161/STROKEAHA.121.038099
117. Sargurupremraj M, Suzuki H, Jian X, Sarnowski C, Evans TE, Bis JC, Eiriksdottir G, Sakaue S, Terzikhan N, Habes M, et al; International Network against Thrombosis (INVENT) Consortium. Cerebral small vessel disease genomics and its implications across the lifespan. *Nat Commun*. 2020;11:6285. doi: 10.1038/s41467-020-19111-2
118. Arvanitakis Z, Capuano AW, Leurgans SE, Buchman AS, Bennett DA, Schneider JA. The relationship of cerebral vessel pathology to brain microinfarcts. *Brain Pathol*. 2017;27:77–85. doi: 10.1111/bpa.12365
119. Sam K, Crawley AP, Conklin J, Poublanc J, Sobczyk O, Mandell DM, Venkatraghavan L, Duffin J, Fisher JA, Black SE, et al. Development of white matter hyperintensity is preceded by reduced cerebrovascular reactivity. *Ann Neurol*. 2016;80:277–285. doi: 10.1002/ana.24712
120. Fernando MS, Simpson JE, Matthews F, Brayne C, Lewis CE, Barber R, Kalaria RN, Forster G, Esteves F, Wharton SB, et al; MRC Cognitive Function and Ageing Neuropathology Study Group. White matter lesions in an unselected cohort of the elderly: molecular pathology suggests origin from chronic hypoperfusion injury. *Stroke*. 2006;37:1391–1398. doi: 10.1161/01.STR.0000221308.94473.14
121. Kapasi A, Yu L, Petyuk V, Arfanakis K, Bennett DA, Schneider JA. Association of small vessel disease with tau pathology. *Acta Neuropathol*. 2022;143:349–362. doi: 10.1007/s00401-021-02397-x
122. Shi Y, Thrippleton MJ, Makin SD, Marshall I, Geerlings MI, de Craen AJM, van Buchem MA, Wardlaw JM. Cerebral blood flow in small vessel disease: a systematic review and meta-analysis. *J Cereb Blood Flow Metab*. 2016;36:1653–1667. doi: 10.1177/0271678X16662891
123. Wardlaw JM, Makin SJ, Valdes Hernandez MC, Armitage PA, Heye AK, Chappell FM, Muñoz-Maniega S, Sakka E, Shuler K, Dennis MS, et al. Blood-brain barrier failure as a core mechanism in cerebral small vessel disease and dementia: evidence from a cohort. *Alzheimers Dement*. 2017;13:634–643. doi: 10.1016/j.jalz.2016.09.006
124. van der Veen PH, Muller M, Vincken KL, Hendrikse J, Mali WPTM, van der Graaf Y, Geerlings MI; SMART Study Group. Longitudinal relationship between cerebral small-vessel disease and cerebral blood flow: the second manifestations of arterial disease-magnetic resonance study. *Stroke*. 2015;46:1233–1238. doi: 10.1161/STROKEAHA.114.008030
125. Nam KW, Kwon HM, Jeong HY, Park JH, Kwon H, Jeong SM. 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. doi: 10.1161/HYPERTENSIONAHA.119.12830
126. Carnevale L, D'Angelosante V, Landolfi A, Grillea G, Selvetella G, Storto M, Lembo G, Carnevale D. Brain MRI fiber-tracking reveals white matter alterations in hypertensive patients without damage at conventional neuroimaging. *Cardiovasc Res*. 2018;114:1536–1546. doi: 10.1093/cvr/cvy104
127. Carnevale L, Maffei A, Landolfi A, Grillea G, Carnevale D, Lembo G. Brain Functional Magnetic resonance imaging highlights altered connections and functional networks in patients with hypertension. *Hypertension*. 2020;76:1480–1490. doi: 10.1161/HYPERTENSIONAHA.120.15296
128. Shen J, Tozer DJ, Markus HS, Tay J. Network efficiency mediates the relationship between vascular burden and cognitive impairment: a diffusion tensor imaging study in UK Biobank. *Stroke*. 2020;51:1682–1689. doi: 10.1161/STROKEAHA.119.028587
129. Siedlinski M, Carnevale L, Xu X, Carnevale D, Evangelou E, Caulfield MJ, Maffia P, Wardlaw J, Samani NJ, Tomaszewski M, et al. Genetic analyses identify brain structures related to cognitive impairment associated with elevated blood pressure. *Eur Heart J*. 2023;44:2114–2125. doi: 10.1093/eurheartj/ehad101
130. Azarpazhooh MR, Avan A, Cipriano LE, Munoz DG, Sposato LA, Hachinski V. Concomitant vascular and neurodegenerative pathologies double the risk of dementia. *Alzheimers Dement*. 2018;14:148–156. doi: 10.1016/j.jalz.2017.07.755
131. Love S, Miners JS. Cerebrovascular disease in ageing and Alzheimer's disease. *Acta Neuropathol*. 2016;131:645–658. doi: 10.1007/s00401-015-1522-0
132. Sweeney MD, Sagare AP, Zlokovic BV. Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. *Nat Rev Neurol*. 2018;14:133–150. doi: 10.1038/nrneurol.2017.188
133. van Dijk SE, Drenth N, Hafkemeijer A, Labadie G, Witjes-Ané MW, Blauw GJ, Rombouts Serge ARB, van der Grond J, van Rooden S. Neurovascular coupling in early stage dementia: a case-control study [published online November 22, 2023]. *J Cereb Blood Flow Metab*. doi: 10.1177/0271678X231214102. https://doi.org/10.1177/0271678X231214102
134. Gottesman RF, Schneider AL, Zhou Y, Coresh J, Green E, Gupta N, Knopman DS, Mintz A, Rahmim A, Richey Sharrett A, et al. Association between midlife vascular risk factors and estimated brain amyloid deposition. *JAMA*. 2017;317:1442–1450. doi: 10.1001/jama.2017.3090
135. Lane CA, Barnes J, Nicholas JM, Sudre CH, Cash DM, Parker TD, Malone IB, Lu K, James S-N, Keshavan A, et al. Associations between blood pressure across adulthood and late-life brain structure and pathology in the neuroscience substudy of the 1946 British birth cohort (Insight 46): an epidemiological study. *Lancet Neurol*. 2019;18:942–952. doi: 10.1016/S1474-4422(19)30228-5
136. van Arendonk J, Neitzel J, Steketee RME, van Assema DME, Vrooman HA, Segbers M, Ikram MA, Vernooij MW. Diabetes and hypertension are related to amyloid-beta burden in the population-based Rotterdam Study. *Brain*. 2023;146:337–348. doi: 10.1093/brain/awac354
137. Cooper LL, O'Donnell A, Beiser AS, Thibault EG, Sanchez JS, Benjamin EJ, Hamburg NM, Vasan RS, Larson MG, Johnson KA, et al. Association of aortic stiffness and pressure pulsatility with global Amyloid-β and regional Tau Burden among Framingham heart study participants without dementia. *JAMA Neurol*. 2022;79:710–719. doi: 10.1001/jamaneurol.2022.1261
138. Hu H, Meng L, Bi YL, Zhang W, Xu W, Shen XN, Ou YN, Ma YH, Dong Q, Tan L, et al. Tau pathologies mediate the association of blood pressure with cognitive impairment in adults without dementia: The CABLE study. *Alzheimers Dement*. 2022;18:53–64. doi: 10.1002/alz.12377
139. Sible IJ, Nation DA; Alzheimer's Disease Neuroimaging Initiative. Visit-to-visit blood pressure variability and CSF Alzheimer Disease biomarkers in cognitively unimpaired and mildly impaired older adults. *Neurology*. 2022;98:e2446–e2453. doi: 10.1212/WNL.0000000000200302
140. Faraco G, Park L, Zhou P, Luo W, Paul SM, Anrather J, Iadecola C. Hypertension enhances Aβ-induced neurovascular dysfunction, promotes β-secretase activity, and leads to amyloidogenic processing of APP. *J Cereb Blood Flow Metab*. 2016;36:241–252. doi: 10.1038/jcbfm.2015.79
141. Faraco G, Hochrainer K, Segarra SG, Schaeffer S, Santisteban MM, Menon A, Jiang H, Holtzman DM, Anrather J, Iadecola C. Dietary salt promotes cognitive impairment through tau phosphorylation. *Nature*. 2018;574:686–690. doi: 10.1038/s41586-019-1688-z
142. Schreiber S, Drukarch B, Garz C, Niklass S, Stanaszek L, Kropf S, Bueche C, Held F, Vielhaber S, Attems J, et al. Interplay between age, cerebral small vessel disease, parenchymal amyloid-β, and tau pathology: longitudinal studies in hypertensive stroke-prone rats. *J Alzheimers Dis*. 2014;42:S205–S215. doi: 10.3233/JAD-132618
143. Liu J, Liu S, Matsumoto Y, Murakami S, Sugakawa Y, Kami A, Tanabe C, Maeda T, Michikawa M, Komano H, et al. Angiotensin type 1a receptor deficiency decreases amyloid β-protein generation and ameliorates brain amyloid pathology. *Sci Rep*. 2015;5:12059. doi: 10.1038/srep12059
144. Kurata T, Lukic V, Kozuki M, Wada D, Miyazaki K, Morimoto N, Ohta Y, Deguchi K, Ikeda Y, Kamiya T, et al. Telmisartan reduces progressive accumulation of cellular amyloid beta and phosphorylated tau with inflammatory responses in aged spontaneously hypertensive stroke resistant rat. *J Stroke Cerebrovasc Dis*. 2014;23:2580–2590. doi: 10.1016/j.jstrokecerebrovasdis.2014.05.023
145. Wang J, Ho L, Chen L, Zhao Z, Zhao W, Qian X, Humala N, Seror I, Bartholomew S, Rosendorff C, et al. Valsartan lowers brain beta-amyloid protein levels and improves spatial learning in a mouse model of Alzheimer disease. *J Clin Invest*. 2007;117:3393–3402. doi: 10.1172/JCI31547
146. Loot AE, Schreiber JG, Fisslthaler B, Fleming I. Angiotensin II impairs endothelial function via tyrosine phosphorylation of the endothelial nitric oxide synthase. *J Exp Med*. 2009;206:2889–2896. doi: 10.1084/jem.20090449
147. Nguyen H, Chiasson VL, Chatterjee P, Kopriva SE, Young KJ, Mitchell BM. Interleukin-17 causes Rho-kinase-mediated endothelial dysfunction and hypertension. *Cardiovasc Res*. 2013;97:696–704. doi: 10.1093/cvr/cvs422
148. van Veluw SJ, Hou SS, Calvo-Rodriguez M, Arbel-Ornath M, Snyder AC, Frosch MP, Greenberg SM, Bacskai BJ. Vasomotion as a driving force for paravascular clearance in the awake mouse brain. *Neuron*. 2020;105:549–561.e5. doi: 10.1016/j.neuron.2019.10.033
149. Harrison IF, Ismail O, Machhada A, Colgan N, Ohene Y, Nahavandi P, Ahmed Z, Fisher A, Meftah S, Murray TK, et al. Impaired glymphatic function and clearance of tau in an Alzheimer's disease model. *Brain*. 2020;143:2576–2593. doi: 10.1093/brain/awaa179
150. Mestre H, Tithof J, Du T, Song W, Peng W, Sweeney AM, Olveda G, Thomas JH, Nedergaard M, Kelley DH. Flow of cerebrospinal fluid is driven by arterial

pulsations and is reduced in hypertension. *Nat Commun*. 2018;9:4878. doi: 10.1038/s41467-018-07318-3
151. Mortensen KN, Sanggaard S, Mestre H, Lee H, Kostrikov S, Xavier ALR, Gjedde A, Benveniste H, Nedergaard M. Impaired glymphatic transport in spontaneously hypertensive rats. *J Neurosci*. 2019;39:6365–6377. doi: 10.1523/JNEUROSCI.1974-18.2019
152. Holstein-Rønsbo S, Gan Y, Giannetto MJ, Rasmussen MK, Sigurdsson B, Beinlich FRM, Rose L, Untiet V, Hablitz LM, Kelley DH, et al. Glymphatic influx and clearance are accelerated by neurovascular coupling. *Nat Neurosci*. 2023;26:1042–1053. doi: 10.1038/s41593-023-01327-2
153. Carnevale D, Mascio G, D'Andrea I, Fardella V, Bell RD, Branchi I, Pallante F, Zlokovic B, Yan SS, Lembo G. 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. doi: 10.1161/HYPERTENSIONAHA.112.195511
154. Fang F, Yu Q, Arancio O, Chen D, Gore SS, Yan SS, Yan SF. RAGE mediates Aβ accumulation in a mouse model of Alzheimer's disease via modulation of β- and γ-secretase activity. *Hum Mol Genet*. 2018;27:1002–1014. doi: 10.1093/hmg/ddy017
155. Chen J, Mooldijk SS, Licher S, Waqas K, Ikram MK, Uitterlinden AG, Zillikens MC, Ikram MA. Assessment of advanced glycation end products and receptors and the risk of dementia. *JAMA Netw Open*. 2021;4:e2033012. doi: 10.1001/jamanetworkopen.2020.33012
156. Zhang W, Zhou Y, Wang J, Gong X, Chen Z, Zhang X, Cai J, Chen S, Fang L, Sun J, et al. Glymphatic clearance function in patients with cerebral small vessel disease. *Neuroimage*. 2021;238:118257. doi: 10.1016/j.neuroimage.2021.118257
157. Grodstein F, Leurgans SE, Capuano AW, Schneider JA, Bennett DA. Trends in Postmortem neurodegenerative and cerebrovascular neuropathologies over 25 years. *JAMA Neurol*. 2023;80:370–376. doi: 10.1001/jamaneurol.2022.5416
158. Tzourio C, Dufouil C, Ducimetière P, Alpérovitch A. Cognitive decline in individuals with high blood pressure: a longitudinal study in the elderly. EVA Study Group. Epidemiology of Vascular Aging. *Neurology*. 1999;53:1948–1952. doi: 10.1212/wnl.53.9.1948
159. Haag MD, Hofman A, Koudstaal PJ, Breteler MM, Stricker BH. Duration of antihypertensive drug use and risk of dementia: a prospective cohort study. *Neurology*. 2009;72:1727–1734. doi: 10.1212/01.wnl.0000345062.86148.3f
160. McGrath ER, Beiser AS, DeCarli C, Plourde KL, Vasan RS, Greenberg SM, Seshadri S. Blood pressure from mid- to late life and risk of incident dementia. *Neurology*. 2017;89:2447–2454. doi: 10.1212/WNL.0000000000004741
161. Hughes D, Judge C, Murphy R, Loughlin E, Costello M, Whiteley W, Bosch J, O'Donnell MJ, Canavan M. Association of blood pressure lowering with incident dementia or cognitive impairment: a systematic review and meta-analysis. *JAMA*. 2020;323:1934–1944. doi: 10.1001/jama.2020.4249
162. Rashid T, Li K, Toledo JB, Nasrallah I, Pajewski NM, Dolui S, Detre J, Wolk DA, Liu H, Heckbert SR, et al. Association of intensive vs standard blood pressure control with regional changes in cerebral small vessel disease biomarkers: post hoc secondary analysis of the SPRINT MIND randomized clinical trial. *JAMA Netw Open*. 2023;6:e231055. doi: 10.1001/jamanetworkopen.2023.1055
163. Sible IJ, Nation DA. Blood pressure variability and cognitive decline: a post hoc analysis of the SPRINT MIND trial. *Am J Hypertens*. 2023;36:168–175. doi: 10.1093/ajh/hpac128
164. Peters R, Xu Y, Fitzgerald O, Aung HL, Beckett N, Bulpitt C, Chalmers J, Forette F, Gong J, Harris K, et al; Dementia rIsk REduCTion (DIRECT) Collaboration. Blood pressure lowering and prevention of dementia: an individual patient data meta-analysis. *Eur Heart J*. 2022;43:4980–4990. doi: 10.1093/eurheartj/ehac584
165. van Rijssel AE, Stins BC, Beishon LC, Sanders ML, Quinn TJ, Claassen JAHR, de Heus RAA. Effect of antihypertensive treatment on cerebral blood flow in older adults: a systematic review and meta-analysis. *Hypertension*. 2022;79:1067–1078. doi: 10.1161/HYPERTENSIONAHA.121.18255
166. Beaman EE, Bonde AN, Larsen SMU, Ozenne B, Lohela TJ, Nedergaard M, Gíslason GH, Knudsen GM, Holst SC. Blood-brain barrier permeable β-blockers linked to lower risk of Alzheimer's disease in hypertension. *Brain*. 2023;146:1141–1151. doi: 10.1093/brain/awac076
167. Freeman MW, Halvorsen YD, Marshall W, Pater M, Isaacsohn J, Pearce C, Murphy B, Alp N, Srivastava A, Bhatt DL, et al; BrigHTN Investigators. Phase 2 trial of baxdrostat for treatment-resistant hypertension. *N Engl J Med*. 2023;388:395–405. doi: 10.1056/NEJMoa2213169
168. Desai AS, Webb DJ, Taubel J, Casey S, Cheng Y, Robbie GJ, Foster D, Huang SA, Rhyee S, Sweetser MT, et al. Zilebesiran, an RNA interference therapeutic agent for hypertension. *N Engl J Med*. 2023;389:228–238. doi: 10.1056/NEJMoa2208391
169. Kisler K, Nelson AR, Montagne A, Zlokovic BV. Cerebral blood flow regulation and neurovascular dysfunction in Alzheimer disease. *Nat Rev Neurosci*. 2017;18:419–434. doi: 10.1038/nrn.2017.48
170. Toth P, Tucsek Z, Sosnowska D, Gautam T, Mitschelen M, Tarantini S, Deak F, Koller A, Sonntag WE, Csiszar A, et al. Age-related autoregulatory dysfunction and cerebromicrovascular injury in mice with angiotensin II-induced hypertension. *J Cereb Blood Flow Metab*. 2013;33:1732–1742. doi: 10.1038/jcbfm.2013.143
171. Bell RD, Winkler EA, Sagare AP, Singh I, LaRue B, Deane R, Zlokovic BV. Pericytes control key neurovascular functions and neuronal phenotype in the adult brain and during brain aging. *Neuron*. 2010;68:409–427. doi: 10.1016/j.neuron.2010.09.043
172. Kisler K, Nelson AR, Rege SV, Ramanathan A, Wang Y, Ahuja A, Lazic D, Tsai PS, Zhao Z, Zhou Y, et al. Pericyte degeneration leads to neurovascular uncoupling and limits oxygen supply to brain. *Nat Neurosci*. 2017;20:406–416. doi: 10.1038/nn.4489
173. Drury ER, Wu J, Gigliotti JC, Le TH. Sex differences in blood pressure regulation and hypertension: renal, hemodynamic, and hormonal mechanisms. *Physiol Rev*. 2024;104:199–251. doi: 10.1152/physrev.00041.2022