# Hypertension and the Brain: A Risk Factor for More Than Heart Disease

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## Introduction

As our life expectancy increases and the proportion of older adults in our population grows, cognitive changes emanating from cerebrovascular disease are becoming an increasingly common problem. With disease progression, these cognitive changes often transition into dementia, gradually leading to decreased quality of life and a considerable burden of care for other members of the

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family and the community. While Alzheimer's disease (AD) is the most prevalent cause of dementia, cerebrovascular disease has been increasingly accepted as the second most common etiology of vascular cognitive impairment and dementia worldwide. Cerebral small vessel disease (cSVD), a group of pathological processes affecting the small arteries, arterioles, venules, and capillaries of the brain, is not only a major contributor to stroke in humans but also an important cause of vascular and mixed dementia [1, 2]. The clinical manifestations of cSVD comprise a wide range of symptoms including signs typical of stroke onset, neurological deficits ranging from mild to progressive cognitive decline, dementia, depression, and physical disabilities [3]. Especially, the overlap of risk factors accounting for AD and cSVD makes their clinical differentiation often challenging [4]; thus, the estimated proportion of dementia caused by cSVD ranges between 36 and 67% [5]. Regardless of the medical, social and economic importance, specialized treatments are missing due to poor understanding of the disease pathogenesis.

It has become evident that vascular risk factors contribute to the pathogenesis of cSVD and hence, the development of cognitive impairment [6, 7]. Among them, hypertension emerges as a major modifiable risk factor for cerebral complications. Pathological changes in BP have been directly linked to cognitive decline, which initiated controversial discussions about BP control as a potential therapeutic strategy to achieve optimal brain perfusion and thus, reduce the occurrence of a mild stage of cognitive impairment preceding both AD and vascular dementia [8, 9]. Yet, the underlying mechanisms linking hypertension to cognitive decline and specifically, to cSVD have not yet been fully elucidated, which makes the search for effective therapies challenging.

## Cerebrovascular Dysfunction during cSVD and Hypertension and Its Consequences for the Brain

The unspecific arteriopathy typical for cSVD is characterized by hypertrophy, endothelial dysfunction, enlarged perivascular spaces [10] and enhanced permeability, resulting in micro-bleedings, subcortical lacunar infarctions and diffuse areas of white-matter lesions [11, 12]. Microscopic infarcts and microbleeds have been associated with cognitive dysfunction accompanying vascular pathologies such as leukoaraiosis, lacunar infarcts, large infarcts, as well as with AD [7]. Number and location of such microscopic infarcts are major determinants of cognitive dysfunction [13], whereby a cortical and subcortical location is commonly associated with dementia [14, 15]. Vascular changes underlying cSVD likely include inflammatory events that result in endothelial failure and neurovascular unit dysfunction [16]. Immune cells infiltrate the central nervous system (CNS) in many neurodegenerative disorders, in which their participation has critical influence on outcomes such as cerebrovascular responsiveness and brain perfusion, microglial activation and hence, neuronal dysfunction, neuro-inflammation and -degeneration [17]. Leukocyte migration modifies the permeability of the neurovascular unit and marks an early event in vascular injury [18].

During hypertension, the cerebral microcirculation can be compromised in various ways, ranging from functional changes affecting vasomotor capacity, usually modifying blood flow transiently, to complete physical damage resulting from conditions like thrombosis [19]. Subsequent critical global or regional cerebral perfusion deficits cause a suppression of brain activity and cognitive dysfunction [20]. Besides, inflammation can deteriorate the vessel wall through impairing endothelial function, which results in reduced functionality of the microvasculature that can render the cells it nourishes ischemic, and, if sustained, lead to irreversible neuronal damage [21]. Hypertension-associated cerebral microbleeds are typically located in basal ganglia, thalamus, brain stem, and cerebellum, while a lobar distribution is frequently linked to cerebral amyloid angiopathy [22]. Diffuse white-matter damage or leukoaraiosis are also attributable to high systolic BP, and indicate a reduction in white-matter density possibly translating into impaired cognitive functioning [23]. White-matter lesions are thought to evolve from a combination of demyelination, lacunar infarcts and axonal loss and are not only associated with ischemic and hemorrhagic stroke but also with dementia, especially with deficits in motor speed and executive functions [24, 25]. Interestingly, hypertension has also been correlated to increased amounts of amyloid-β deposited in the brain of ApoE4 carriers as people with both the risk allele and high BP accumulated significantly more amyloid-β than normotensive ApoE4 controls [26]. Interestingly, the use of antihypertensive medication reduced amyloid-β deposition suggesting an interaction between a gene and a vascular risk factor. Nevertheless, the mechanism that ties ApoE4 to hypertension remains unclear, but hypertension's negative effects on blood-brain barrier (BBB) integrity might promote the observed increase in amyloid-β deposition in hypertensive ApoE4.

## Mechanisms Underlying Hypertension-Associated Cerebrovascular Dysfunction

The microcirculation plays an important role in the pathophysiology of hypertension since primarily small arteries and arterioles determine peripheral resistance. Enhanced vasoconstriction, compromised vasodilatation, increased wall-to-lumen ratio associated with reduced lumen diameter, and rarefaction of small arteries, alone or in combination, promote the increase of total peripheral resistance and mean BP values. Likewise, the loss of elastic fiber integrity through the degeneration of elastin fibers and a concurrent deposition of stiffer collagen promote an increased vascular fragility and arterial stiffness [27, 28]. Vascular calcification resulting from oxidative stress and inflammatory processes, in which pro-inflammatory cytokines like tumor necrosis factor alpha (TNF-α) play a crucial role, equally compromises arterial elasticity and hence, functionality with deleterious consequences [29, 30]. Adding to these structural factors, reduced availability of endothelial nitric oxide further stimulates arterial stiffness not only by contributing to a pro-constrictive state but also by fueling hypertrophy [31]. Independent of its basis, the resulting amplified large artery stiffness leads to elevated central systolic and pulse pressures that, when transmitted into cerebral arteries, potentially lead to remodeling and a progressive impairment of the arterial lumen. Augmented arterial pulse pressure due to large artery stiffening can result in the development of white-matter lesions [32] since especially, the terminal white-matter arterioles are susceptible targets for pressure-induced structural alterations [33]. These structural alterations may support a chronic hypoxic state through impaired vascular function, and increase the risk of long-term disability.

BP varies markedly during normal daily activities. To adequately respond to the BP variations without detrimental effects on cerebral blood flow (CBF), cerebral arterioles adjust their resistance according to intravascular pressure [34]. Thus, CBF remains constant over a wide range of BP changes. This plateau phase is determined by upper and lower limits, which are shifted to higher BP values during chronic hypertension to maintain the same level of CBF [35]. Within the cerebrovascular tree, a gradient of myogenic activity exists; proximal arteries exhibit marginal myogenic tone, whereas more distal sections possess a substantially higher myogenic activity [36, 37]. However, under pathologic conditions, proximal arteries also present augmented myogenic tone, resulting in CBF alterations [37–39]. Even if under such conditions global perfusion is maintained, regional perfusion deficits may occur, leading to local hypoxia-induced tissue damage. To date, most studies describing the effect of hypertension on the cerebral microvasculature comprised large intracranial arteries such as the middle cerebral artery [40, 41], while less attention has been paid to smaller vessels [37, 39] or even to parenchymal arterioles [42, 43]. Since especially these small arteries and arterioles possess higher myogenic responsiveness compared to larger vessels [44] hypertension could negatively affect their structure and/or function to an extent that might cause white matter lesions and concomitantly, lead to the development of vascular cognitive impairment [45].

The exact mechanisms how hypertension affects autoregulation are not completely understood but they likely include a combination of myogenic tone alterations and artery remodeling. At times of elevated intraluminal pressure, wall thickness increases to maintain artery wall stress within a physiological range generally leading to reduced lumen diameter and increase in wall-to-lumen ratio. In hypertension, the typical inward remodeling of cerebral arteries together with increased myogenic tone may limit auto-regulation of CBF. A consecutive reduction of CBF potentially increases the likeliness of for instance, the development of ischemic situations with deleterious consequences for oxygen tension that, when permanently reduced, might also affect neuronal structures furthest away from the capillary surface. Patients with exaggerated variability of BP are at increased risk of ischemic insults and silent strokes [46], which suggests that recurring acute or permanent hypoperfusion could favor brain damage and the occurrence of cognitive impairment. Indeed, CBF measurements in patients with ischemic leukoaraiosis revealed significantly reduced CBF within deep white-matter [47, 48].

Besides structural alterations, hypertension also provokes abnormally low densities of arterioles and capillaries. Vessel rarefaction might be causative to a reduction in CBF and hence, increasing the risk of cognitive decline in patients with hypertension [49]. Although not directly shown in experimental hypertension, a mouse model of small vessel disease revealed capillary loss in white-matter regions prior to the occurrence of any overt reduction in CBF or visible white-matter injury [45]. Yet, there are no studies documenting cerebral artery rarefaction in hypertensive patients although capillary rarefaction appears to be a regular complication with implications for deleterious end-organ damage apart from the brain [19, 50]. Further experimental studies are needed to elucidate upon the possible involvement of cerebral

vessel rarefaction in the hypertensive brain especially, since studies showed that pro-angiogenic and anti-hypertensive therapies enhanced vessel density [51, 52].

### Endothelial Involvement in Hypertension-Mediated Cerebrovascular Dysfunction

Endothelial cells (ECs) that determine the interface between circulating blood and vessel wall are conferred essential significance in the maintenance of vascular integrity, regulation of vascular tone and hence, adequate tissue perfusion [53]. Endothelium-derived vasoactive factors participate in the maintenance of resting CBF by coordinating the vasodilatation and the response to mechanical forces [54]. They furthermore concert the increase in CBF upon brain activation, the so-called functional hyperemia, which is attenuated in patients with chronic hypertension and has been associated to reduced cognitive function [55, 56]. It is well known that compromised endothelial function in patients with hypertension results in reduced vasodilation, increased vascular tone and thrombo-inflammation [40, 41, 56, 57], but whether this represents a key aspect in symptomatic lacunar stroke and cSVD remains to be determined. However, the functional impairment of the endothelium appears to be an early indicator of vascular dysfunction in small and large vessel disease [58, 59]. Unfortunately, the direct assessment of endothelial function in the human brain is challenging, which limits the number of available studies to a few. A recent study analyzed measurements of cerebral and peripheral vessel reactivity in response to $CO_2$ inhalation using transcranial Doppler and duplex ultrasound in patients with lacunar stroke and control subjects [60]. Here, abnormalities in peripheral artery reactivity seemed to be related to vascular risk factors, and severity of endothelial dysfunction in cerebral arteries correlated with the occurrence of lacunar stroke in patients with cSVD [60]. Impaired endothelial function has been furthermore shown by assessing endothelial nitric oxide signaling in patients with lacunar infarction and associated cSVD [61, 62]. Endothelial-derived nitric oxide predominantly contributes to the regulation of local vascular tone and BP by promoting vasodilatory responses, while also mediating anti-inflammatory and anti-thrombotic effects by inhibiting leukocyte adhesion and platelet aggregation [63, 64]. The disruption of endothelium-dependent nitric oxide signaling may be promoted by oxidative stress, driven primarily by the NADPH oxidases that have been implicated in cerebral vascular dysfunction associated with cSVD risk factors and cerebral amyloid angiopathy [65–67]. Reactive oxygen species (ROS) are key mediators of cerebrovascular dysfunction in hypertension, as they contribute to vessel rarefaction and structural remodeling of cerebral blood vessels and hence, lead to functional alterations with profound consequences for CBF. Specifically, experimental studies comprising rodent models of hypertension report that targeting the ROS producing enzyme NADPH oxidase or its assembly protects from cerebrovascular oxidative stress and consequently, from alterations in endothelium-dependent relaxation and functional hyperemia [65, 68, 69]. To date, existing studies showing the direct effect of hypertension on cerebral artery tone [43, 70] mostly describe endothelial dysfunction in isolated artery approaches; only a few studies show a direct link between endothelium-dependent vasodilation and CBF. Moreover, histological analyses of post-mortem tissue from patients with severe cSVD present evidence of an intact endothelial layer in small arteries in the frontal white-matter, while showing an apparent loss of myocytes and other mural cells [71, 72]. Specifically, pericyte loss and basement membrane thickening link risk factors, such as ageing, hypertension and diabetes with functional disturbances in CBF and with cSVD [73]. This complexity makes further experimental approaches to illuminate upon the vasodilatory capacity of small cerebral arteries exposed to high BP before and during overt cSVD necessary.

### Endothelial Activation and BBB Involvement

In blood vessels, EC integrity is a primary target for mechanotransduction-dependent challenges. In a variety of vascular-based pathologies, the link between intercellular junctions and the cytoskeleton is frequently disrupted or impaired causing the loss of proper mechanotransduction signaling and most importantly, a destabilization of the endothelial barrier function [74]. Cerebral ECs possess a particularly low transport capacity preventing substance entry into the brain. The integrity of the BBB is therefore of essential importance to maintain the homeostasis of the cerebral microenvironments and hence, normal brain function.

The imbalance between vasoactive substances as well as chronic disturbances in hemodynamic forces caused by, for instance, hypertension lead to endothelial activation, a prerequisite for thrombo-inflammation and an early indicator of BBB impairment that is mostly accompanied by the elevation of adhesion molecules orchestrating leuko-

cyte rolling, adhesion and migration [18]. Peripheral markers of endothelial activation like soluble vascular cellular adhesion molecule-1, soluble intercellular adhesion molecule-1 (sICAM-1), sP-selectin, and sE-selectin associate with cSVD-related MRI markers and reduced cognitive performance in patients with essential hypertension, indicating a role of endothelial activation in the pathogenesis of hypertension-mediated cSVD [75, 76]. Independently, sICAM-1 levels appear to be an essential marker for lacunar stroke, early neurological deterioration and in patients with white-matter lesions [61, 77]. However, since it may not be exclusively of endothelial origin, sICAM-1 fails to provide strong support for correlating endothelial activation and vascular-based cognitive impairment. Other, more specific, endothelial activation markers emerged from studies showing an independent relationship between sE-selectin and the number of microbleeds in patients with cSVD [16]. Despite existing evidence linking endothelial activation and cSVD, the fact that elevated circulating markers of endothelial activation in patients with cSVD may derive from any vascular bed permits direct association of cerebro-endothelial activation, inflammation-induced artery stiffening and resulting impairment of auto-regulation of CBF. Nevertheless, there is evidence showing elevation of adhesion molecules, leukocyte rolling along cerebral vessels and T-cells infiltration and accumulation in perivascular spaces during hypertension that suggest a causative link between endothelial activation and cerebrovascular dysfunction [78–80].

EC activation has also been conferred with regulatory function during exocytosis of P-selectin, tissue plasminogen activator and von Willebrand factor (vWF) [18]. Especially, vWF expression is elevated in both chronic and acute inflammation. Its augmentation in patients with lacunar infarcts aligns with findings correlating a prothrombotic status with markers of cSVD in elderly hypertensive patients [81]. Thrombo-inflammation promotes vessel occlusions and endothelial-mediated vascular injuries leading to increased BBB permeability, triggering further damage of the vessel wall and finally resulting in vessel ruptures [82]. Such endothelial-based sites of leakage have been discussed as early endothelial injury promoting the impairment of the BBB in a model of hypertension-induced cSVD [82]. BBB impairment resulting from alterations of its cellular components has been described to occur during neurodegenerative diseases [83], but was also associated with cSVD and lacunar infarcts [84, 85]. However, it remains elusive whether BBB dysfunction is the primary cause for changes to happen in the cerebral microvasculature, since to date, studies only reported an increased BBB permeability at times of clinically evident cSVD [84]. Nevertheless, increasing numbers of activated circulating immune cell, endothelial activation and the presence of activated microglia in the CNS of hypertensive individuals suggest a link between chronically elevated BP and BBB impairment.

## Conclusions

Hypertension elicits multiple negative effects on the vasculature with devastating consequences for auto-regulation of CBF. Local disturbances in CBF lead to brain lesions affecting important white-matter tracts and manifesting as complete and incomplete infarcts, microbleeds and white-matter hyperintensities. Since hypertension has a direct negative effect on the vasomotor function of cerebral arteries that is comparable to that observed in other cardiovascular pathologies, the risk of cerebrovascular damage and cognitive decline mediated through hypertension need to be considered for future experimental studies and clinical trials. Recent findings among participants in the Framingham Heart Study showing that the incidence of dementia has declined over the course of 3 decades [86] give rise to the hope that the burden of dementia is decelerating. However, the observed dependency on education in particular does not reduce the urgency to unravel the mechanistic link between hypertension and cognitive decline. Recent randomized controlled trials examined the impact of anti-hypertensive therapy on cognitive performance with conflicting results. A meta-analysis of longitudinal studies showed that anti-hypertensive treatment reduces the risk of the development of cognitive decline and vascular dementia but failed to reverse the already established hypertension-associated cognitive dysfunction [87].

Increasing evidence indicating that vascular dementia and AD share common pathogenic mechanisms mediated by vascular risk factors [88], highlights the urgency to understand underlying mechanisms of hypertension-induced cerebrovascular complications leading to cSVD and associated cognitive impairment in order to identify and isolate effective therapeutic targets that can prevent and most importantly reverse cognitive decline mediated by hypertension.

## Disclosure Statement

None.

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