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## Cognition and Hemodynamics

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### Abstract

The relationship between cerebral hemodynamics and cognitive performance has increasingly become recognized as a major challenge in clinical practice for older adults. Both diabetes and hypertension worsen brain perfusion and are major risk factors for cerebrovascular disease, stroke and dementia. Cerebrovascular reserve has emerged as a potential biomarker for monitoring pressure–perfusion–cognition relationships. Endothelial dysfunction and inflammation, microvascular disease, and macrovascular disease affect cerebral hemodynamics and play an important role in pathophysiology and severity of multiple medical conditions, presenting as cognitive decline in the old age. Therefore, the identification of cerebrovascular vascular reactivity as a new therapeutic target is needed for prevention of cognitive decline late in life.

### Keywords

hemodynamics; brain atrophy; cognition; aging; blood flow; hypertension; hypotension; diabetes mellitus

### Introduction

The relationship between cerebral hemodynamics and cognitive outcomes in aging has gained more attention because of the growing elderly population worldwide. Recently, the link between midlife cardiovascular risk factors and late-life dementia has been recognized as a potential pathway to early diagnosis of people at risk of dementia. Hypertension and diabetes are the most prevalent vascular risk factors. Hypertension affects more than a third of the world's population [1], and 16.2 % people have hypotension [2]. Diabetes affects 366 million people, and this number is expected to rise to 552 millions by 2030 [3;4]. Among those who are older than 65 years, 65% to 75% have hypertension, [5] and 26% have diabetes, and these numbers are expected to rise as the global population ages.

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#### Competing interests

The author declares no competing interests

#### Review criteria

This article is based on a comprehensive search of full-text English-language articles in the PubMed database, with search terms including “brain atrophy in aging,” “perfusion,” “cognition,” “diabetes mellitus,” “white matter hyperintensities,” “hypotension and cognition,” “blood pressure and dementia” “antihypertensive therapy” ; “endothelial dysfunction” and “angiotensin receptor” The reference lists of the articles identified during this search were checked for additional articles published from January 2005-till May 2012.

#### Author contributions

V. Novak contributed to discussion of content for the article, researched data to include in the manuscript, reviewed and edited the manuscript prior to submission and revised the manuscript in response to the peer-reviewers' comments.

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The combination of advanced age with hypertension, diabetes and other risk factors provides a background for multifaceted interactions in pathophysiological pathways that lead to dementia. Furthermore, abnormalities in cerebral hemodynamics during midlife may contribute to late life cognitive decline. Alternative mechanisms such as genetic predisposition, inflammation, autonomic failure, and neurodegenerative changes associated with Alzheimer's disease, Parkinsonism dementia, Lewy Body dementia, or acute brain infarctions or hemorrhage may contribute to the progression of dementia.

Although the pathophysiology of the relationship between cerebral hemodynamics, cerebrovascular reserve and cognition is complicated [6], altered neurovascular coupling resulting in small vessel disease, regional hypoperfusion and neurodegeneration has emerged as one of the pathways linking cardiovascular risk factors to cognitive decline [7–10]. Evidence from Physiological monitoring, transcranial Doppler ultrasound (TCD) and magnetic resonance imaging (MRI) bring supports linking altered vasoreactivity to cognition. Therefore, focus on improvement of endothelial function may provide new therapeutic approaches for the prevention of cognitive decline in aging population.

### Brain vascular reserve

Cerebral vasoregulation is a dynamic process that redistributes cerebral blood flow (CBF) toward the brain areas in need of increased perfusion. Vasoreactivity reflects the ability of microvasculature to adapt to a changing microenvironment, fluctuating metabolic demands such as oxygen and glucose delivery and blood pressure (BP) variations. It reflects endothelium-mediated responses at the neurovascular unit and beyond, thus regulating local, regional and global perfusions [11–13] that adjust to concomitant changes in neuronal activity and vascular tone [14]. This concept, known as neurovascular coupling, is a process in which neurons and other cells such as astrocytes and glial cells interact with endothelial cells, capillaries and blood vessels and thus facilitate the relationship among neuronal activity, hemodynamic factors, and cell-to-cell signaling [15]. These interactions allow for synchronized increases in neuronal activity and perfusion, and thus make possible communication within brain regions and functional networks.

Via neurogenic, metabolic, and myogenic regulation, neurovascular coupling enables to coordinate CBF redistribution to brain regions with increased metabolic demands, along with adjustments to beat-to-beat changes in transmural pressure and vasomotor tone. Neurogenic control refers to tonic and phasic activity within the central autonomic network, which includes noradrenergic, serotonergic, cholinergic and dopaminergic signaling that modulate vasomotor tone, endothelial function and signaling among functional neuronal networks. Metabolic regulation, which is mediated by molecules such as O<sub>2</sub>, CO<sub>2</sub>, ATP, and glucose, among other factors, refers to the adjustment of cellular metabolisms to changes in metabolic activity and fluctuating glycemic levels, whether in tandem or in isolation. Myogenic regulation refers to changes in endothelium-myocytes to induce contraction and relaxation of the vessel wall due to increases of intramural pressure within each heart beat.

### Evaluation of cerebrovascular reserve

The ability of the neurovascular units within vascular territories and the whole brain to respond to variation in BP and intracranial pressure and to increased metabolic demands is referred to as the brain vascular reserve. Two well-described and extensively-investigated cerebral hemodynamic indices in both human and animal models are cerebrovascular reactivity to CO<sub>2</sub>, or acetazolamide, [16–19] and cerebral autoregulation, or pressure regulation [20–23]. Both mechanisms compensate for changing metabolic demands and arterial pressure on account of various physiological and pathological conditions. [17;20–22;24]. Several noninvasive techniques can be used to assess autoregulation and CO<sub>2</sub>

vasoreactivity, as well as vascular and functional responses to other stimuli, such as TCD, near infrared spectroscopy (NIRS), 3D-arterial spin labeling (3D-CASL) MRI, blood-oxygen-level dependent (BOLD) MRI, 2D-time of flight MR angiography, single-photon emission computed tomography (SPECT), and positron emission tomography (PET). These methods, however, reference different parameters such as blood flow or flow velocity within larger vessels, blood volume or tissue perfusion; they use different variables; and also have different temporal and spatial resolutions. Therefore, estimates of vasomotor reserve may differ greatly between these approaches.

## Autoregulation

Cerebral perfusion cannot be predicted from BP alone on account of the non-linear pressure-flow relationship due to autoregulation; this is in contrast to the linear or curvilinear relationship between pressure and flow in non-autoregulatory tissues. "Autoregulation" most commonly refers to CBF adaptation to acute and chronic changes in arterial BP and perfusion pressure. Pressure autoregulation maintains a fairly-stable perfusion over the range of mean systemic pressures 60–150 mmHg. Static autoregulation refers to long-term "steady-state" control, whereas dynamic autoregulation refers to the adaptation of perfusion to beat-to-beat variations in intracranial pressure and BP [25]. Many medical conditions are associated with autoregulatory impairment, such as hypertension, hypotension [26], diabetes mellitus (DM) [27], vascular disease, smoking, and stroke [28;29]. Even in healthy people, autoregulation may fail if BP falls below the lower limits during acute conditions such as syncope. With impaired autoregulation, the sigmoid autoregulation curve, which expresses the relationship between CBF and mean BP, becomes more linear, and perfusion becomes pressure-dependent. Figure 1 illustrates this concept.

Chronic hypertension and hypotension alter CBF autoregulation and may affect the autoregulatory range. Orthostatic and postprandial hypotension are defined as a 20 mmHg decline in systolic BP or as a 10 mmHg decline in diastolic BP when in an upright position, or within one hour after a meal [30]. DM is the most common cause of autonomic failure, where altered BP regulation is characterized by supine hypertension and orthostatic and/or postprandial hypotension. Therefore, the mean BP range may vary greatly from > 180 mm Hg in supine position to 80 mm Hg in upright position.

TCD is commonly used as a noninvasive assessment of static and dynamic autoregulation using beat-to-beat recordings of BP and blood flow velocity (BFV) [31] at baseline and during interventions such as standing up or head-up tilt [19;32]. Three patterns of autoregulatory responses were identified using a regression analysis approach in patients with autonomic failure and orthostatic hypotension; narrowed autoregulation range; normal autoregulation; and expanded autoregulation over a wide range of BP (mean BP 110–180 mmHg) [26]. With normal autoregulation, regression analyses have shown no correlation between BP and BFV, while with expanded autoregulation BP and BFV remained highly correlated but the slope of regression line was flat. Therefore, BFV declined only mildly and was usually maintained in upright position. The autoregulation curve in hypertension was shifted to the right toward higher BP values, and therefore lower limits of autoregulation occurred at lower BP levels. With this shift, the autoregulation window narrows and the slope of the CBF–BP curve becomes steeper. In this setting, vasodilatation responses to low BP may be reduced, especially with atherosclerosis, and vasoconstriction responses to high BP may be increased, due to endothelial activation and higher sympathetic tone. In autoregulatory failure, BP and BFV are strongly correlated, marked by a steep regression slope, which results in a rapid decline in BFV even with small reductions in BP. Therefore, in an upright position BP may fall below the range of effective regulation, and perfusion decreases. As suggested by the above autoregulatory patterns, daily activities such as sitting,

standing up, or eating a meal may reduce BFV and potentially induce hypoperfusion [33], which could lead to syncope [34], falls, or ischemia and cognitive changes [35].

Dynamic autoregulation is often assessed from spontaneous fluctuations in BP and BFV [31] at baseline and during interventions such as the Valsalva maneuver, standing up or head-up tilt. [19;32] CBF fluctuations at 0.01–0.03 Hz were linked with intracranial pressure [36], central sympathetic activity [37], microcirculation, and cerebral oxygenation [38]. Autoregulation is quantified using mathematical modeling, Fourier transform analysis, coherence function, and more-recently-developed nonlinear methods [22;27;39;40]. A substantial phase lead of CBF velocities with respect to the peripheral BP indicates intact autoregulation [31;41;42]. Nonlinear approaches, such as multiple coherence [19] and multimodal pressure-flow (MMPF), enable assessment of autoregulation at multiple time scales and have greater sensitivity and specificity to defects in autoregulation than do linear methods [27;40]. An application of the MMPF method demonstrates, for example, that hypertension and DM significantly impair autoregulation to an observable degree after an ischemic stroke [40]. Mathematical modeling has been increasingly used to assess time-dependent relationships between BP, BFV and intracranial pressure and volume to predict cerebrovascular capacity and flow reserve controlled by autoregulation, perfusion pressure and cerebrospinal fluid production and reabsorption [43].

### **CO<sub>2</sub> vasoreactivity**

Carbon dioxide (CO<sub>2</sub>) is a potent vasodilator stimulus that modulates vascular tone during normal breathing, slow breathing while awake and during sleep, and hyperventilation. CO<sub>2</sub> vasoreactivity is measured from CBF or BFV responses to vasoconstrictive and vasodilatory stimuli. Examples of vasoconstrictive stimuli include hypocapnia and hyperventilation, while vasodilatory stimuli include CO<sub>2</sub> rebreathing, breath holding, slow breathing, and acetazolamide administration [44]. Vasoreactivity is calculated as the percent flow change per CO<sub>2</sub> change. Blood flow increases linearly over the physiological, range of the end-tidal CO<sub>2</sub> from 25–50 mm Hg. Measurements of CO<sub>2</sub> vasoreactivity using TCD are commonly used in clinical and ambulatory settings, because of their feasibility. Imaging technique advancements based on 3D CASL MRI [45;46] BOLD MRI, and SPECT imaging, however, enable the assessment of vasoreactivity in anatomical regions and vascular territories [47]. Though these techniques present advantages over TCD by providing a better regional distribution of vasoreactivity, they lack temporal resolution and utilize values averaged over minutes.

### **Cerebral blood flow mapping using CASL MRI**

3D CASL (CASL) enables noninvasive measurement of regional perfusion and is increasingly used to quantify perfusion and vasoreactivity (mL/100g/min) using established protocols and previously-described methods [48–51]. With this technique, labeling of inflowing arterial water is achieved by the application of optimized time-varying magnetic fields. The naturally-occurring hydrogen nuclei of water become the label which then decays with the MR longitudinal relaxation time T<sub>1</sub> (approx. 1.4 seconds in blood). A labeled image is subtracted from an unlabeled image to measure CBF. Measurement of the tissue-dependent T<sub>1</sub> and use of established theory [52;53] permit the calculation of absolute blood flow into tissue [54]. Images are acquired with pseudo-continuous labeling, background suppression and a volumetric stack of spirals fast spin echo acquisition [48]. Cerebral blood flow maps are normalized for regional tissue volume that allows calculations of regional CBF and construction of vasoreactivity maps, and adjustment for regional tissue loss. The CO<sub>2</sub> vasoreactivity is computed as the slope of the linear fit between CO<sub>2</sub> and CBF values among baseline, hypocapnia and hypercapnia in each region as an absolute change, a percentage change, or both. Using this approach, vasodilation and vasoconstriction reserve

can be calculated as absolute and relative differences from baseline [46]. Cerebral vasoreactivity differs among major vascular territories and is region-specific; it is higher in the parietal-occipital regions in comparison to the frontal and temporal regions and the insular cortex. Regions with lower vasodilatory capacity may be more affected by hypoperfusion and chronic hypoxia than those with higher capacities [45;46]. Cardiovascular risk factors such as hypertension [55], diabetes [45] and stroke [46] alter regional perfusion at baseline and also affect regional vasoreactivity in the fronto-temporal and parieto-occipital cortical regions. Typically, vasodilatation reactivity, such as the ability to augment perfusion, is reduced with diabetes, while vasoconstriction reactivity, the ability reduce perfusion, is preserved or even exaggerated [46;50]. Importantly, vasoreactivity correlates with gray matter volume and functional cognitive measures in these regions (e.g. fronto-temporal and parietal areas). In diabetic subjects, hypertension, higher systolic BP and retinopathy were further associated with lower baseline perfusion and vasodilatation reactivity.

### **Cerebromicrovascular disease, vasoreactivity and brain atrophy**

Cerebromicrovascular disease associated with hypertension, diabetes and other cardiovascular risk factors, including age, is linked with regional hypoperfusion and brain volume loss, as well as with neuronal degeneration and cognitive decline in elderly people [56–61] Cerebromicrovascular disease accelerates age-related CBF declines [62–65] and is associated with regional differences in cerebral vasoregulation and reserve capacity [66]. Aging, hypertension, diabetes mellitus, or stroke reduce vasodilatation [45;67] in multiple vascular territories, whereas vasoconstriction can be preserved [46]. The variability of CBF responses to pathogenic stimuli underscores the importance of underlying small and large vessel disease that may lead to chronic hypoperfusion in numerous brain regions. Measurements of CBF augmentation in response to hypercapnia using TCD [68;69] and an intravenous or inhalation<sup>133</sup> Xe method [70] suggest that cerebrovascular reserve and CO<sub>2</sub> reactivity are impaired in persons with type 2 DM when compared to healthy controls, and declined further with DM duration [68] and severity [66]. Hyperglycemia levels were negatively correlated with CO<sub>2</sub> reactivity and response to phenylephrine infusion-induced BP elevations [69]. Improper DM control with hemoglobin A1c (HbA1c) >10% was associated with more severe albuminuria, acute hyperglycemia, higher von Willebrand factor activity, and marginally-higher neuropathic scores, but it was not associated with changes in global cerebrovascular reactivity. These findings suggest that cerebrovascular reserve impairment may be regional and conditional on structural changes of resistance arteries or metabolic factors [71] in specific brain regions. A higher pulsatility index also indicates an increased intracranial vascular resistance and microvascular damage in DM [72].

Recent advances in ultra-high-field MR has allowed unprecedented resolution and enabled the visualization of microvascular diseases such as lacunar infarctions, microinfarctions, microbleeds, iron deposits, and diffused white matter hyperintensities (WMHs) with unprecedented resolution [73–76]. Figure 2 demonstrates small vessel disease and aptterns of abnormal microvascularture that occur with hypertension.

Microinfarcts and iron deposits in brain tissue associated with altered blood brain barrier BBB in patients with hypertension were previously invisible in lower-resolution scans [75;77]. WMHs common in MRIs of older adults are often associated with global and regional brain atrophy, including hippocampal atrophy [64]; reduced functional neuronal mass, which indicates that an active neurodegenerative process has taken place [78]; lower perfusion [79] and metabolism in the white matter, preferentially affecting frontal, parietal, and temporal cortices [80]; lower oxygenation in the frontal lobes [81]; slower CBF

velocities [82]; cognitive decline and executive dysfunction [83]; vascular dementia [84–86]; motor impairment [87]; and depression [88]. The presence of WMHs at baseline was also associated with an increase in diastolic BP over 24 years of the follow-up (>10 mmHg; OR 2.6, 95% CI 1.3–5.1), systolic BP (>40 mmHg; OR 2.0, 95% CI 1.2–3.4), pulse pressure (>24 mmHg; OR 1.8, 95% CI 1.1–2.7), and mean arterial pressure (>6 mmHg; OR 2.2, 95% CI 1.4–3.4) [89].

The pathogenesis of multifocal, as well as, diffuse WMHs in older adults, however, remains unclear [90]. Histopathology of deep periventricular WMHs is heterogeneous, showing partial loss of myelin and axons, astrogliosis, dilatation of perivascular spaces, activated macrophages and fibrohyalinosis [91;92]. Punctuate and diffuse lesions in deep white matter are associated with arteriolosclerotic changes and with incomplete and complete infarctions [93]. In addition, microvascular disease and subcortical WMHs were associated cross-sectionally with cognitive impairment, [58–60] and longitudinally with the rate of cognitive decline [60] among community-dwelling elderly. The strong association of WMHs with diabetes and hypertension [60;94] supports the hypothesis of BBB break down [95]. A subsequent demyelination of white matter may occur independently of perivascular inflammation in the gray matter.

Subcortical WMHs have been associated with cognitive impairment at baseline [59;60;86] and also longitudinally with the rate of cognitive decline [60]. Older people with large subcortical WMHs have higher systolic BP, reduced cerebral metabolism, and worsened cognitive performance [96;97]. This evidence further suggests that the multifactorial pathways leading to WMHs also affect perfusion in the gray matter and white matter, and converge on neuronal death, cortical and subcortical white matter disconnection, and that this process can precede functional decline for many years. The associative areas of the frontal and temporal cortices and limbic circuits, which are involved in complex tasks, such as, decision-making, and memory, that have high demands on perfusion and energy supply are preferentially affected by neuronal death [98]. Other mechanisms and genetic predisposition (such the *ApoEε4* genotype), however, are also involved and may further alter blood flow regulation and contribute to WMHs, deposition of amyloid  $\beta$  A4 protein and neurofibrillary tangles, altered cholinergic transmission. The interplay among these mechanisms is complex and poorly understood. For example, clearance of amyloid  $\beta$  A4 protein from the brain is dependent on vascular reactivity, which in turn is affected by small vessel disease. Therefore, DM and hypertension and other conditions associated with small vessel disease may contribute to the pathology of Alzheimer's disease [99–103]. Recently, it was shown that the vascular defects in APOE-deficient and *ApoE4*-expressing mice precede neuronal dysfunction and may initiate neurodegenerative changes. Astrocyte -secreted *ApoE3*, but not *ApoE4*, suppressed the CypA-nuclear factor- $\kappa$ B-matrix-metalloproteinase-9 pathways in pericytes through lipoprotein receptors, resulting in blood-brain barrier BBB breakdown, and initiation neuronal cell death. More studies are needed to determine whether these results translate into neurodegeneration in humans [104].

### **Endothelial dysfunction, inflammation and vasoreactivity**

Age-related endothelial dysfunction and risk factors such as hypertension and DM set the stage for altered neurovascular coupling and regional decline in vasomotor capacity [66]. Endothelial dysfunction is associated with vascular inflammation due to glucotoxicity, lipotoxicity and neurotoxicity affecting neurons, astrocytes and endothelial cells. Microangiopathy alters vessel permeability [105;106] and vasoreactivity [69], but its severity may differ between peripheral and cerebral circulation, as well as between organ systems. With DM, adaptive neovascularization such as capillary density, arteriogenesis and intratree anastomoses is diminished in the peripheral circulation, contributing to cardiac and renal diseases [107]. In contrast, neovascularization in the brain may be augmented yet still

dysfunctional [107]. This condition manifests as an increased media-lumen ratio, a compromised BBB and increased activity of matrix metalloproteinases (MMP) [108]. Therefore, inflammation-activated microglial cells and invading macrophages play important roles in altered neurovascular coupling, BBB permeability and, ultimately, neuronal loss. The combined effects of cardiovascular risk factors induce oxidative stress in mitochondria [109;110] and the endoplasmic reticulum, which triggers the release of pro-inflammatory cytokines and activation of pro-apoptotic pathways [111]. This cascade leads to endothelial dysfunction, decreased synthesis of nitric oxide and sympathetic activation [111], and culminates in a decline in vasodilatory reactivity [12]. Vasoconstriction responses may be exaggerated through the activation of sympathetic vasomotor fibers and endothelin-1 pathways [111]. Adhesion molecules are concomitant with altered endothelial cell motility through nitric oxide dependent pathways [112;113], angiogenic activity and neovascularization [114]. The regional effects of hyperglycemia on neurovascular coupling, metabolism, and neuronal function are dependent on energy demands [115–117]. Therefore, cognitive and motor regions with high metabolic rates [118;119] are particularly vulnerable to hyperglycemia and vascular inflammation [120;121]. Recently, it has been shown that serum intercellular adhesion molecules [ICAM] and vascular cell adhesion molecules [VCAM] are associated with altered vasoreactivity and gray matter atrophy in several brain regions in older diabetic but also in non-diabetic hypertensive adults [50], and that cell adhesion molecules were also associated with worsened cognition. Notably, gray matter brain volume loss was not related to other cytokines such as tumor necrosis factor alpha [TNF $\alpha$ ], C-reactive protein [CRP], endothelin-1, or interleukins 1-6 [IL1-6], which suggests that CAMs may serve as new serum markers of endothelial dysfunction in the brain [50]. The relationship between adhesion molecules, impaired vasoreactivity and atrophy may indicate an ongoing inflammation-remodeling process of activated endothelium, marking degeneration and angiogenesis in the affected cortical regions. Thus, in the presence of DM and other cardiovascular risk factors (e.g. obesity, hypertension, hypercholesterolemia, and metabolic syndrome), increased oxidative stress and inflammation may lower the intrinsic threshold for cell survival [122] and accelerate aging and atrophy in the affected regions.

### Midlife risk factors and cognitive decline in old age

The actual relationship between age and cognition in senescence, however, might be predictable over the course of a lifespan if neurovascular coupling is considered a variable acting on cerebral vasoregulation in response to BP and metabolic factors. Mounting evidence suggests that the association of endothelial dysfunction, microvascular disease, and macrovascular disease may have an important role in the manifestation and severity of multiple medical conditions underlying cognitive decline late in life. Figure 3 illustrates the conceptual model of pathways by which cardiovascular risk factors (hypertension, obesity, diabetes) may alter brain perfusion and ultimately lead to brain atrophy and functional decline.

The size of the aging population is increasing exponentially, while the obesity and diabetes epidemics are still on the rise. Cognitive decline, slow gait speed, and falls are all common manifestations of the subcortical frontal dysfunction that occurs frequently with aging. There is growing evidence that DM accelerates the aging process in the brain [103;123–125]. There is also increasing evidence for the relationship between BP pressure regulation through the lifespan and cognitive deterioration and dementia later in life [126–131]. Diabetes and BP dysregulation have been linked not only with Alzheimer's disease pathophysiology and vascular dementia, first and second most common types of dementia but also with mild cognitive impairment (MCI). The involvement of vascular mechanisms such as strokes, lacunar infarcts, small vessel disease, and cardiovascular diseases in vascular dementia underscores the importance of altered neurovascular coupling in these

pathologies. [132] A diagnosis of MCI is distinct from that of dementia. A person diagnosed with MCI has abnormal cognitive function with objective and subjective markers of cognitive deterioration, although there may be minimal to no impact on the complex functions of daily living. Impaired [133;134].

Older adults have shown distinct patterns of decline in verbal fluency and figural recognition. Better performance is associated with greater regional CBF in the inferior temporal gyrus and inferior parietal lobe [135–137] However, CBF in these regions declines with age, and individuals with a steeper decline had worse cognitive performance. A positive association between CBF and motor performance was also seen in the sensory-motor regions in the pre- and postcentral gyrus. Participants with faster reaction times had better CBF in the parahippocampal region and hippocampus. Faster performance on the figural task was related to greater CBF in the insula and decreased CBF in the middle frontal gyrus, while slower performance on this task was associated with decreased CBF in the superior and middle temporal gyri, regions associated with visuospatial processing [135–137]. The Framingham Heart Study group cardiovascular disease risk profile score (FCRP) was used to prospectively assess the relationship between baseline cardiovascular risk and subsequent changes in resting state CBF and brain tissue volumes over the 8-year follow-up in 97 cognitively-normal older participants from the Baltimore Longitudinal Study of Aging [135–137]. Voxel-based changes in regional CBF, measured by resting PET and MRI scans, were correlated over time with cognitive outcomes such as a verbal fluency test and FCRP composite score, as well as its individual components age, cholesterol, BP, smoking status, and type 2 DM. Higher baseline FCRP scores were associated with faster decline in regional CBF in the orbitofrontal, medial frontal and anterior cingulate, insular, precuneus, and brain stem regions. Specifically, higher diastolic BP and DM are independently associated with greater CBF decline in the medial frontal, anterior cingulate and insular regions. DM and higher vascular resistance are associated with faster cognitive decline.

Epidemiological studies and clinical trials suggest that risk factors in mid-life, such as obesity, DM and hypertension, increase the risk of cognitive deterioration in old age. Central pattern of abdominal obesity is a major risk factor for type 2 DM. A prospective study of adults 40–69 years old with a 12-year follow-up showed that the most severe central obesity, and hypertension were each related to poorer performance on tests of executive function and visuomotor skills like the Trail-Making Test Part B and visual reproduction and recall tests [138]. Obesity correlated with increased cerebrovascular resistance, particularly in the upright position, slowed CBF velocities, increased systolic BP, and male gender. [139] In the ARIC study, hypertension and DM are associated with a decline in executive function tasks such as verbal learning, recall and fluency, and digit symbol recognition [140]. In the NHANES III study, stroke and the *ApoE4* genotype were independent predictors of verbal memory decline as assessed by the Delayed Word Recall Test. For the Word Fluency Test, metabolic syndrome, hypertension, and stroke were each independently associated with cognitive decline [141]. The Honolulu Aging study shows that high systolic BP (120–140 and 140 mmHg) in midlife increases the risk of late-life dementia. Men who developed dementia had an additional age-adjusted increase in systolic BP of 0.26 mmHg (95% CI 0.01–0.51 mmHg) from midlife to later life. Up to 58% of those with dementia experienced a systolic BP decrease of 10 mmHg in later life [142]. The risk ratio for dementia was lower in patients treated for hypertension than in untreated patients (RR = 0.76, 95% CI 0.65–0.93 and RR = 1.05, 95% CI 0.86–1.27, respectively) [143]. In hypertensives, decreased CBF measured by PET was associated with a decline in Mini Mental State Examination (MMSE) scores over the 3-years of follow up [144].

The relationship between low perfusion and dementia later in life was suspected. The SMART-MR study has shown that cerebral hypoperfusion is among the mechanisms



contributing to dementia [84;145\*]. This study measured CBF using MRI and angiography in 575 patients with atherosclerotic disease. Baseline parenchymal CBF declined from  $52.3 \pm 9.8$  to  $50.7 \pm 10.3$  (ml/min/100ml) after 3–6 years of the follow up. Regression analyses adjusted for age, sex, follow-up time and vascular risk showed that untreated and poorly-controlled hypertension and higher levels of systolic and diastolic BP were associated with CBF decrease. However, within hypertensive patients ( $n = 469$ ), those patients treated with angiotensin receptor blockers (ARBs) did not show CBF decrease as compared to participants using other antihypertensive medications. Type 2 DM is associated with cortical and subcortical atrophy, lacunar infarcts and asymptomatic infarcts [146;147]. Cortical and subcortical atrophy itself is linked with the duration of diabetes and HbA1c and with impaired attention and executive functions, processing speed, and memory.

Figure 4 demonstrates that an older diabetic person has more global and regional atrophy on MR images as compared to non-diabetic adult.

Cortical and subcortical atrophy itself is linked with the duration of diabetes and HbA1c and with impaired attention and executive functions, processing speed, and memory. Cognitive performance is inversely related to atrophy, WMHs and silent infarcts. There is also a moderate relationship among cognitive decline, HbA1c, and DM duration. [61] The population-based Kungsholmen study reported that DM was associated with hazard ratios of 1.5 for dementia, 2.6 (95% CI 1.2 to 6.1) for vascular dementia, and 1.3 for Alzheimer's disease. In patients who were treated with oral antidiabetic medications, the hazard ratio increased to 1.7 (95% CI 1.0 to 2.8) for dementia and to 3.6 (CI 1.3 to 9.5) for vascular dementia. The risk for vascular dementia increased further in DM patients with severe systolic hypertension or heart disease [85]. Most studies suggest that patients with subcortical vascular dementia are more impaired on frontal-executive tasks than memory, such as free recall, but recognition or cued memory is often well-preserved. [148] Therefore, chronic hyperglycemia may worsen age-related vascular dysfunction, thereby leading to early degeneration of associative brain regions with higher metabolic demands involved in cognition or motor control. Increasing evidence shows that subcortical WM degeneration may contribute to slow gait speed, psychomotor slowing, and poor balance in older people even in the absence of peripheral neuropathy. In a study of more than 700 community-dwelling participants from the Cardiovascular Health Study, WMHs were associated with poorer performance on tests of balance using both clinical and dynamic posturography measures [149]. Among 1077 non-demented elderly men and women participating in the Rotterdam Scan Study, [60] those with the most severe diffuse subcortical WMHs scored nearly 1 SD below the mean on tests of psychomotor speed. Whitman et al. [150] demonstrated that the progression of WMHs is associated with falls and poor postural control. Because of the close proximity of frontal-subcortical circuits that control both motor and cognitive functions, it is not surprising that periventricular vascular lesions may cause simultaneous dysfunction in both systems.

Uncontrolled diabetes is associated with adverse effects due to hyperglycemia, small vessel disease, and hypoperfusion of vital organs. Surprisingly, the effects of improved glucose control on coronary and cerebrovascular complications in this population are debated. The optimal range for glycemic control in vulnerable older patients is still not known, and the target HbA1c levels remain debated. Three randomized control trials (ACCORD, ADVANCE, Veterans Affairs Diabetes) have assessed the impact of intensive glucose-lowering therapy on cardiovascular complications and mortality. [151–153] None of these studies were able to demonstrate significant reduction of cardiovascular events or strokes in the intensive therapy group as compared with the control group. The ACCORD trial enrolled 10,251 participants, with primary intensive glucose lowering therapy with embedded lipid and blood pressure controls HbA1c  $<6.0\%$  vs.  $7.0\text{--}7.9\%$ , primary outcomes

(nonfatal myocardial infarction, stroke, and cardiovascular death) [154]. A subset study of this population, Memory in Diabetes (ACCORD-MIND), assessed the primary outcome Digit Symbol Substitution Test (DSST) score, at baseline and at 20 and 40 months after treatment [143]. There was no significant treatment difference in mean 40-month DSST score. The intensive-treatment group had a greater mean total brain volume than the standard-treatment group, but cognitive outcomes were not different. Therefore, these findings do not support the use of intensive glucose lowering therapy for reduction of adverse effects of diabetes on the brain.

### **Regional atrophy and hypoperfusion in diabetes mellitus, hypertension and hypotension**

Previous studies have shown cross-sectionally that regional perfusion in the frontal and temporal lobes and other areas with higher metabolic rates are specifically affected by diabetes [118]. CBF abnormalities were most frequently seen in the fronto-temporal region, followed by the occipital and parietal regions [155], and were more frequent in long-term DM. Hypoperfusion was also related to fluctuating blood glucose and HbA1c levels and to the frequency of hypoglycemia [66;69]. In diabetics, the ratio between regions with normal CBF compared to reduced CBF was lower than in the controls and inversely correlated with systolic BP, total cholesterol, and atherogenic index. These observations suggest that the combination of hyperglycemia with other risk factors for atherosclerosis may accelerate age-related decline in perfusion [119;156]. During hypoglycemia, CBF increased to areas associated with higher metabolic rate, such as the superior frontal cortices and the right thalamus, and decreased to the right posterior cingulate cortex and the right putamen [157;158]. Type 2 DM is associated cross-sectionally with modest cortical and subcortical atrophy, lacunar infarcts and asymptomatic infarcts [86;146;147]. Cortical and subcortical atrophy was linked with diabetes duration and HbA1c and with impaired attention and executive functions, processing speed and memory. In particular, gray matter loss was greater in areas used for memory and language processing, such as the superior temporal and angular gyri. Poorer cognitive performance was associated with more atrophy, WMHs and silent infarcts [61]. Gray matter density declined with elevated lifetime HbA1c levels, DM duration, and diabetic retinopathy. It appears that superior temporal gyri may be particularly vulnerable to diabetes, as suggested by the relationship between HbA1c and atrophy in these regions [159].

**Hypoglycemia**—Intensive glycemic control increases the risk of hypoglycemic episodes, which may also lead to cerebral hypoperfusion, dysautonomia and unawareness of subsequent episodes. During hypoglycemia CBF is increased to areas associated with higher metabolic rate and cognitive and motor processing, such as the superior frontal cortices and the right thalamus, and it is decreased to the right posterior cingulate cortex and the right putamen. [157;158] The reasons for variability in regional CBF responses to hypoglycemia are not well known. More severe hypoglycemia may trigger sympathetic activation, which may in turn lead to cerebral vasoconstriction and hypoperfusion and loss of consciousness. [160] These observations suggest that the combination of hyperglycemia with other risk factors for atherosclerosis may accelerate age-related decline in perfusion. [119;156]

**Hypotension**—The relationship among BP regulation, autonomic failure and dementia later in life is debated. With orthostatic hypotension, cerebral perfusion depends on autoregulation to maintain perfusion at lower BP levels. Among patients with low BP, (systolic BP <120 mmHg, diastolic BP <70 mmHg), orthostatic hypotension increased the odds of cognitive impairment (measured as >1 MMSE score decline) [161]. This effect may be due to a decreased cerebral perfusion, when BP falls below an autoregulated range. In contrast, among patients with hypertension (systolic BP >140 mmHg, diastolic BP >90 mmHg), the presence of orthostatic hypotension reduced the odds of cognitive impairment

(OR = 0.48, 95% CI 0.26–0.90) [162]. This effect may be due to decreased cerebral vasoconstriction, when BP decline to an autoregulated range. In patients with chronic cerebral infarctions, BFVs decline during daily activities such as sitting, standing or a passive head-up tilt, and that these activities may induce recurrent hypoperfusion. [163] Lower perfusion correlates with worse post-stroke outcomes. Therefore, stroke patients may need a higher perfusion pressure to maintain blood flow during daily activities [46]. Lower perfusion also correlates with worsened outcomes in non-stroke diabetic patients [45]. Analogously, diabetic patients may need to maintain glucose and BP levels within a certain range to maintain perfusion and respond adequately to metabolic demands.

The Malmö Preventive Project [164] assessed the relationship between orthostatic hypotension and long-term morbidity in 722 men aged  $52.6 \pm 3.6$  years over a follow-up of  $19 \pm 5.3$  years. Orthostatic hypotension was observed in 9.9% of participants and was independently associated with age, low BMI, hypertension, increased heart rate, antihypertensive treatment, DM, and current smoking. Systolic hypotension was observed in 64.5% of those with hypotension, and was associated with high pulse pressure, and reduced glomerular filtration rate. Men with orthostatic hypotension had an increased risk of coronary events, stroke and all-cause mortality. Those with orthostatic hypotension, both at baseline and at screening during follow-up were at the highest risk of any adverse event. Similarly, hypotension was associated with low MMSE scores ( $<24$ ) in The Helsinki Aging Study [165], which involved 650 people aged 75–85 years.

Furthermore, frailty was also associated with an inability to regulate orthostatic BP and with lower orthostatic heart rate and BP. On average, after 30 seconds of standing, non-frail subjects had recovered 98% of their baseline systolic BP, while pre-frail and frail subjects had recovered 95 and 92%, respectively [166]. The prevalence of Alzheimer's disease is higher among people with systolic BP  $< 130$  mmHg and diastolic BP  $< 70$  mm Hg, as compared to the reference group (systolic BP 130–139 mm Hg) [56;167] The OPTIMA study [124] prospectively evaluated cognitive function using The Cambridge Cognitive Examination (CAMCOG) tool in 235 cognitively healthy participants, 42 with MCI, 141 with Alzheimer disease, and 59 with other dementia syndrome. In patients with Alzheimer disease, the decline in cognitive scores showed a nonlinear, inverted U-shaped dependence on diastolic BP. Both low and high diastolic BP levels ( $<60$  mmHg and  $>110$  mmHg) were related to faster cognitive decline over 5 years of follow-up ( $z = -2.51$ ,  $P = 0.012$ ). These studies suggest that the combination of altered vasoregulation and declining BP later in life may indicate underlying autonomic failure associated with DM, Alzheimer's disease, Parkinsonism dementia, Lewy Body dementia and other disorders. The loss of central regulation of perfusion and autonomic peripheral BP controls may have a broad impact on brain cognitive networks and, ultimately, on morbidity and mortality. The link between these factors, however, remains to be further studied.

## Antihypertensive therapy and cognition

The inconsistencies in these trials, evident in both individual studies and meta-analyses, are likely related to differences in the populations studied, including variation in age and in baseline cognitive function. The cognitive domain of interest and method of assessment in the studies are additional important explanations for this heterogeneity. Many of the trials have used MMSE, a fairly-insensitive and nonspecific measure of cognitive change [168], but hypertension is more likely to be related to executive function than to the overall cognitive performance that the MMSE assesses [169–171]. Pharmacogenetic variation in cognitive responses, study duration, and pharmacokinetic characteristics of antihypertensives are additional factors that lead to heterogeneity in studies of hypertension therapy and cognitive function. A meta-analysis of randomized controlled trials of antihypertensive

therapy in the elderly indicated that BP reduction lowers the risk of stroke (35%), cardiovascular events (27%) and heart failure (50%), but it does not affect mortality [172]. By contrast, smaller BP reductions and lower intensity of therapy were associated with decreased mortality. The US Veteran Affairs prospective study [173] determined that ARBs are more effective in lowering the risk of Alzheimer's disease and dementia compared with the angiotensin-converting-enzyme (ACE) inhibitor lisinopril or other classes of cardiovascular medications. Other trials that assessed the use of ARBs on cognitive function demonstrated a superior effect of this class of drugs (e.g. candesartan, losartan, valsartan) in comparison with the  $\beta$ -blocker atenolol [174] and a combination hydrochlorothiazide and lisinopril [175].

Antihypertensive drugs such as ACE inhibitors like perindopril, and captopril, ARBs such as losartan [174;176] and calcium-channel blockers like nitrendipine may have class-specific effects, and combination therapy might have an increased cognitive protective effect. For example, in the Cardiovascular Health Study, ACE inhibitors that cross the blood-brain barrier provide cognitive protection, which is not observed with ACE inhibitors that do not cross the blood-brain barrier [177]. Even though these studies may differ a common thread emerges; namely, that antihypertensive treatment is protective against vascular diseases and some of their consequences in the brain. The target for BP lowering that would be protective against cognitive decline remains to be determined.

### Central benefits of renin-angiotensin receptor blockade

Evidence from clinical studies suggests that treatment of hypertension using renin-angiotensin receptor blockers may have beneficial effects on endothelial function, and vasoreactivity that go beyond the lowering of BP. The brain renin-angiotensin system regulates systemic responses to chronic stress induced by hyperglycemia, such as sympathetic activation, vasoconstriction, and neuroinflammation. AT1 receptors are abundant in the brain and are located on endothelial cells as well as on the inner side of the BBB [178]. Binding of angiotensin II to AT1 receptors mediates key events in neuroinflammation and neurodegeneration [179]. An important relationship between AT1 receptors and BBB endothelial cells' permeability [180] and ICAM has been reported. Angiotensin II increases vascular permeability by promoting the expression and secretion of vascular endothelial growth factor [181] and induces the expression of endothelial adhesion molecules like cellular adhesion molecules and selectins, thus promoting leukocyte adhesion in arteriolar endothelium [182]. Stimulation of AT1 receptors mediates cell proliferation, fibrosis, vasoconstriction, aldosterone release, and inflammatory response [183]. However, the differences in nitric oxide (NO)-mediated endothelial dysfunction between peripheral macrocirculation and microcirculation and regional cerebral circulation remain unclear.

The AT1 receptor blockade improves cerebrovascular compliance associated with hypertension and inhibits oxidative stress, pathological cerebrovascular remodeling and inflammation [184–186]. That ARB treatment improves BBB permeability suggests the RAS system is also involved in the pathophysiology of endothelial dysfunction and subsequent damage to neural tissue [187]. Systemic ARB treatment inhibits central hypertensive effects, vasopressin secretion, and the drinking response in spontaneously hypertensive rats [188]. AT1 receptors located in the neurovascular unit [180;189] most likely mediate the central effects of ARBs. Candesartan can cross the BBB, down-regulate the central renin-angiotensin system [190], and decrease angiotensinogen and angiotensin converting enzyme mRNA levels in brain tissue [190]. Both losartan and ACE inhibitor enalapril restore vasoreactivity after BBB injury [191;192].

ARBs are well-tolerated and extensively used to treat cardiovascular and metabolic disorders such as hypertension and diabetes, in which inflammation is an integral pathogenic

mechanism, and may have broad benefit for vascular function that are independent of their BP lowering effects. Furthermore, ARB treatment benefits extend beyond BP reduction. Treatment with AT1 receptor antagonists appears to be a major therapeutic avenue for the prevention of small vessel disease and inflammation in the brain [184;186;193].

Major clinical trials have demonstrated that ARBs increase insulin sensitivity and reduce the incidence of DM, independent of their BP effects [184;186;194;195]. In clinical trials, treatment with ARBs improved vascular function and atherosclerosis associated with diabetes [196–198]. In the Losartan Intervention For Endpoint (LIFE) reduction in hypertension study and the Study on Cognition and Prognosis in the Elderly (SCOPE), [199] treatment with ARBs was associated with reduced occurrence of stroke compared to controls, without significant change in all-cause mortality and with decreased new onset of diabetes (RRR 0.80, 95% CI: 0.74–0.86,  $p < 0.00000001$ ) [200]. Treatment with ARBs reduced cognitive decline as measured by the MMSE [199]. In the On TARGET trial of 28,384 participants, ARBs reduced MMSE decline in people with baseline macroalbuminuria [197]. ARBs also decreased depressive symptoms, [201;202] possibly because brain inflammation plays an important role in the pathophysiology of mood disorders [203;204].

Valsartan has many beneficial effects on both peripheral circulation and the brain, by means of its broad anti-inflammatory actions; these effects are independent of BP reduction. In animal studies, valsartan had vascular and neuroprotective effects such as prevention of proteinuria, preservation of renal structure, delayed appearance of brain damage, increased survival under stressful conditions, [205;206] and ameliorated cognitive impairment in diabetic rats [189]. Valsartan has shown beneficial effects on insulin sensitivity, [200] inflammation, [207] vascular reactivity, [208] and cognitive and executive function [209] at the dose of 160 mg once daily (o.d.). Valsartan treatment lowered the incidence of DM in elderly hypertensives (VALUE trial) [200;210–212]. A reduction of inflammation as measured by ICAM and high-sensitivity C-reactive protein was observed after 6 weeks of valsartan treatment (VAL-MARC), [207] but not after treatment with the ACE inhibitortrandorapril [213]. Therefore, the evidence supporting the use of ARBs for treatment of inflammation and endothelial dysfunction in the brain of older diabetic adults is compelling.

## Conclusions

Substantial evidence exists that supports a link between cerebral perfusion and cognition, a relationship that may be mediated by impairment of vascular reserve and microvascular disease. Not only do cardiovascular risk factors exert long-term effects on vascular function and perfusion regulation that may accelerate later functional cognitive loss, but they also directly contribute to brain atrophy and cognitive decline when combined with conditions such as diabetes, hypertension and hypotension.

Enhanced understanding of the effects of cerebral hemodynamics on cognitive performance, can inform the development of effective approaches for the extension of a healthy lifestyle into old age, prevention of cognitive decline, as well as, development of new treatment strategies for cognitive impairment late in life.

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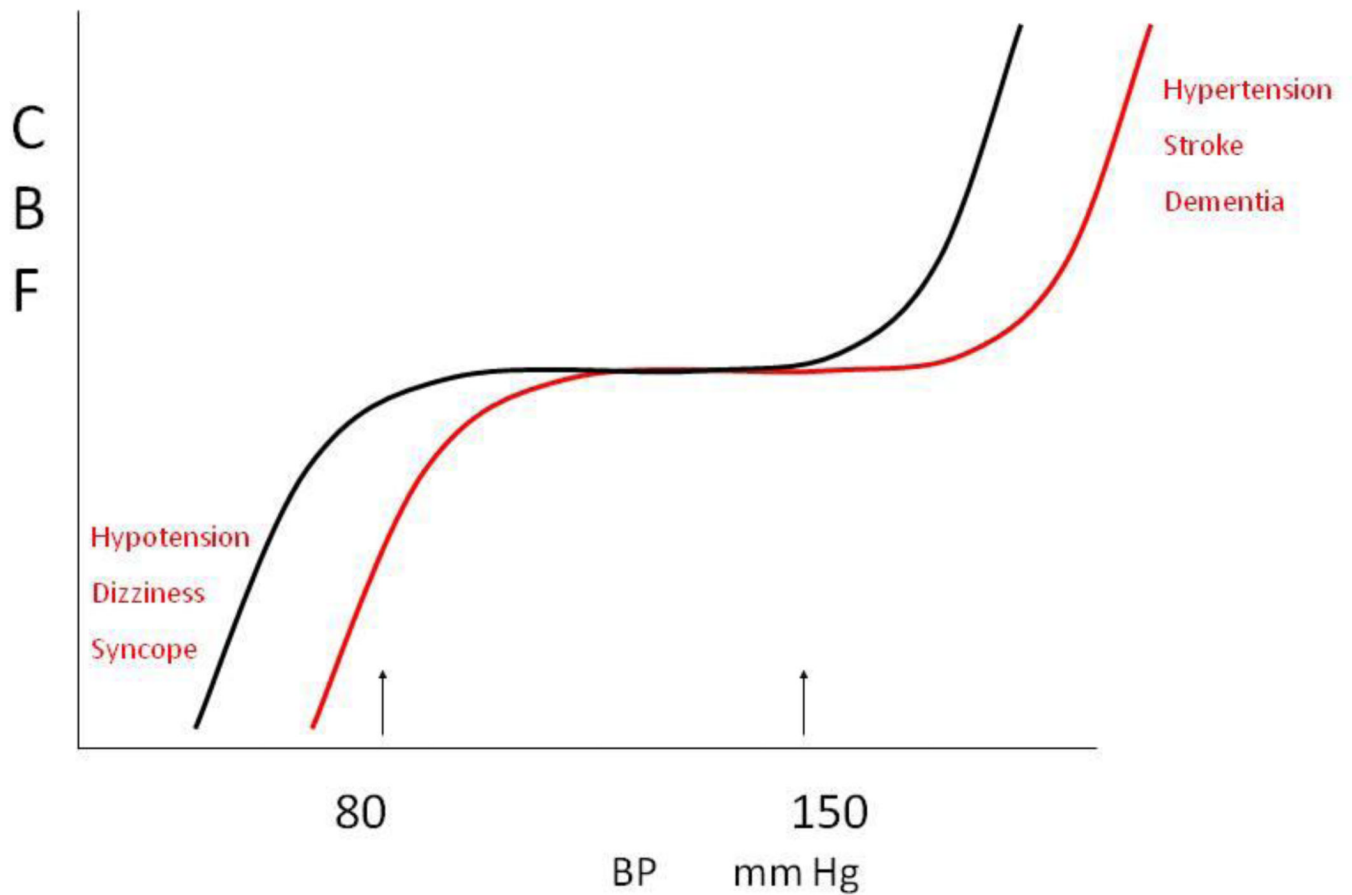
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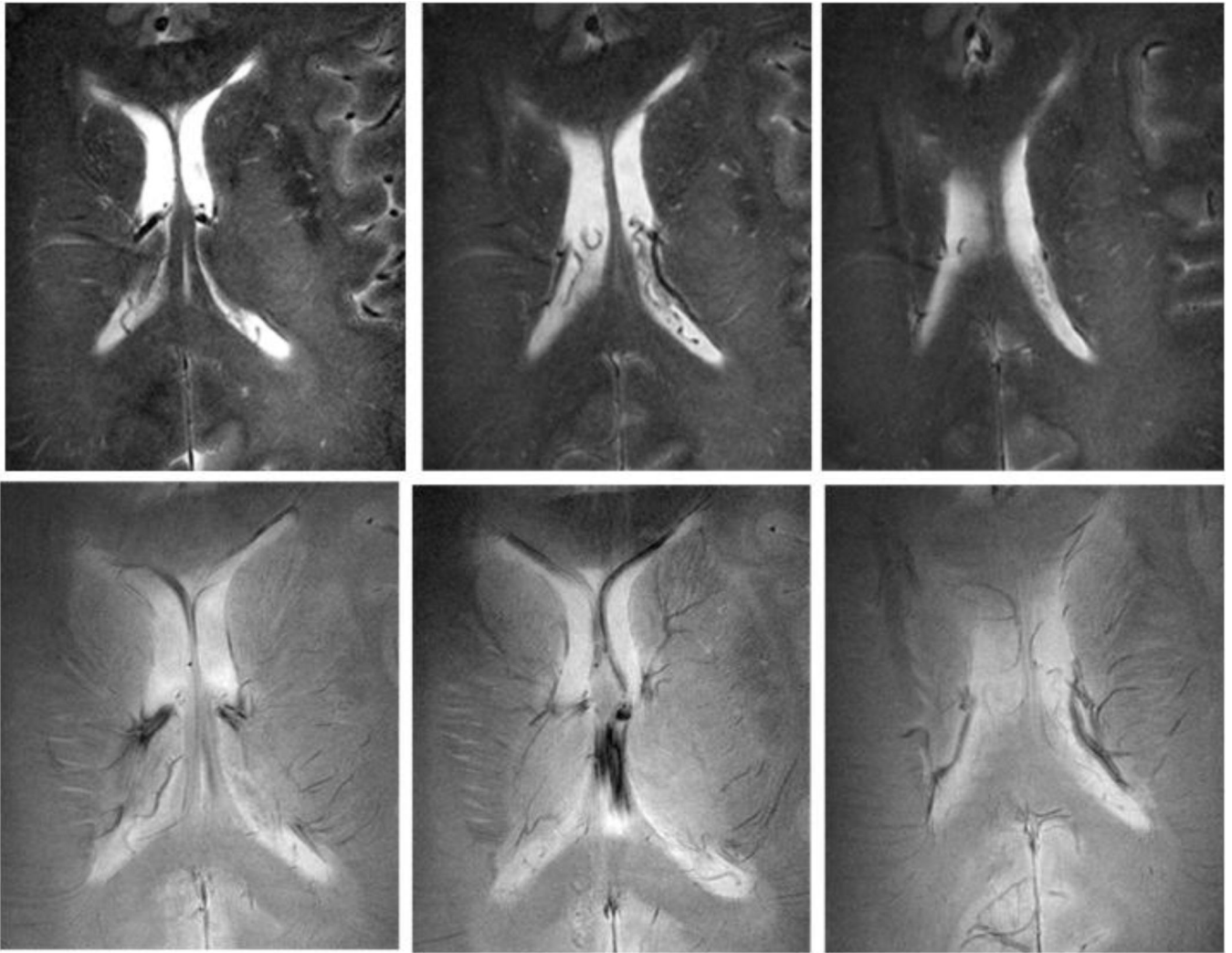


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# Cerebral autoregulation

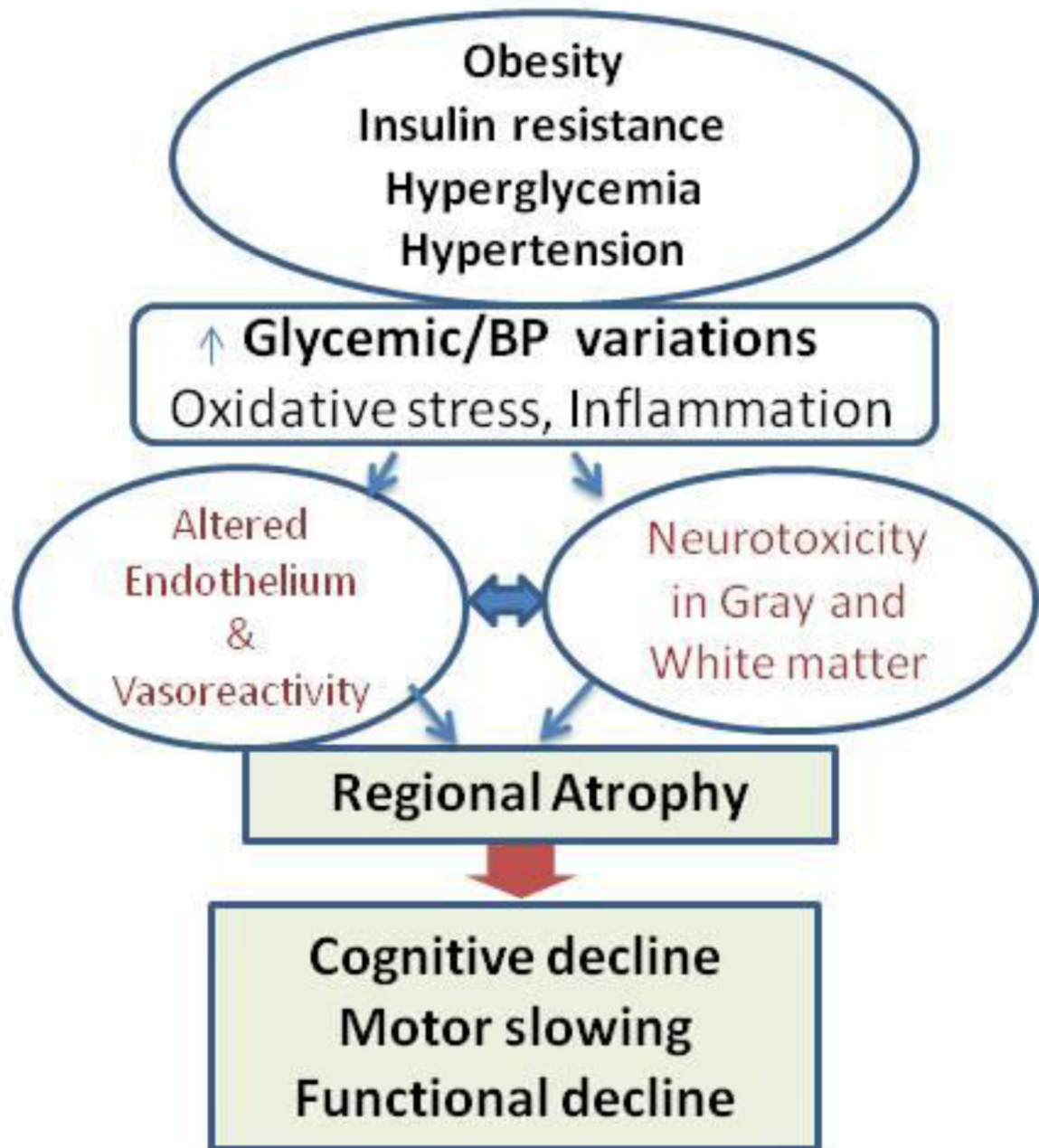


**Figure 1.** Cerebral autoregulation curve- denotes the normal range of pressure -flow regulation (black line) and a right shift of the autoregulation curve toward higher BP values, associated with hypertension (red line).



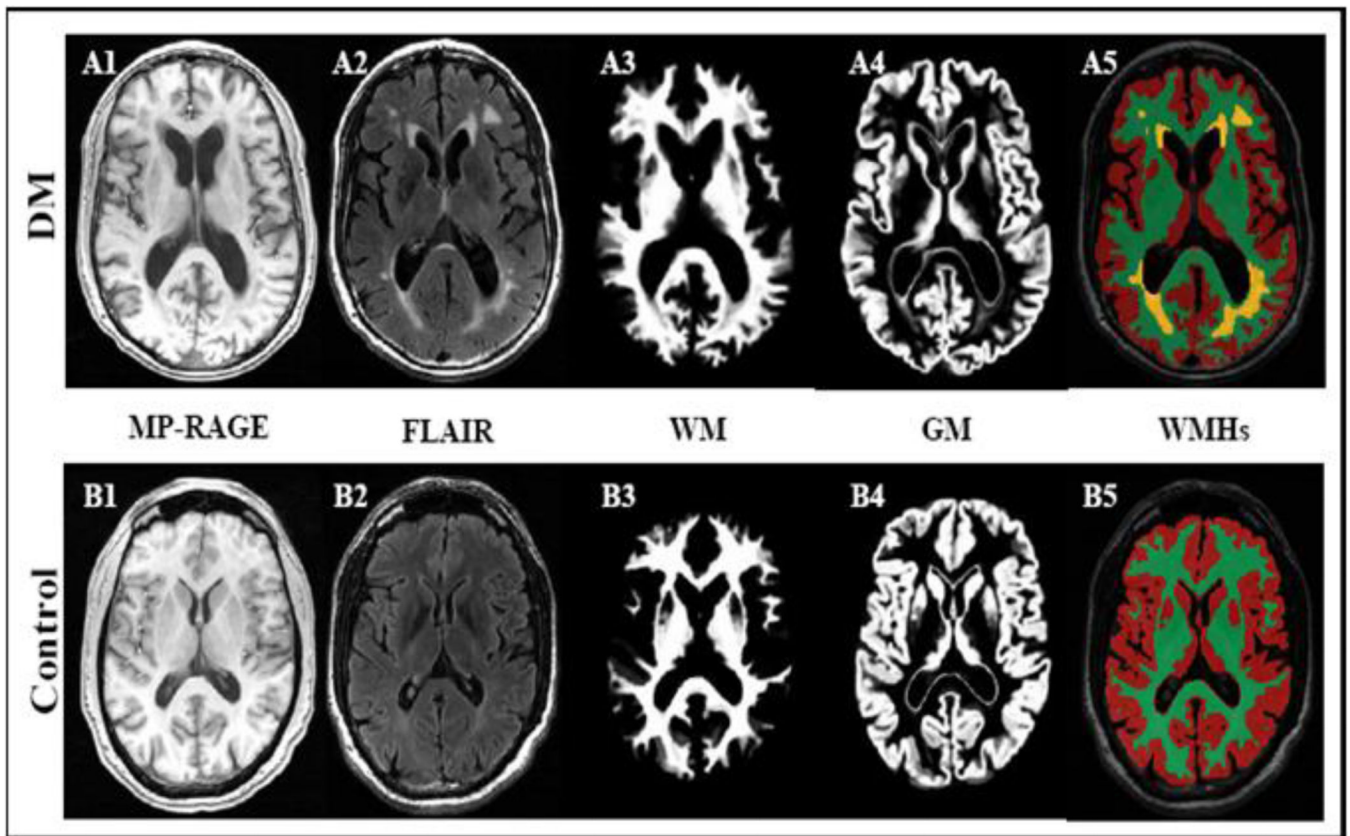
**Figure 2.**

High resolution anatomical images obtained using 8Tesla MRI, a 45-year-old woman with a small vessel disease. Rapid acquisition with relaxation enhancement (RARE) images (A, B, C) at the level of ventricles showed confluent white matter hyperintensities (WMHs) extending from the anterior and posterior horns of the ventricles (white arrows). Additional focal areas of high signal intensity were seen in the periventricular white matter and basal ganglia. 8T GE images (D, E, F) showed normal pattern of microvasculature as signal voids (black arrows). (GE: BW=69.4 kHz, FOV=20×20cm, slice thickness 2.3 mm, TR=600 ms, TE=10 ms, matrix 1024 × 1024; RARE: BW=69.4 kHz, FOV=20 × 20 cm<sup>2</sup>, slice thickness 2 mm, TR=3000 ms, TE=22 ms, matrix 512 × 512, RARE factor 4). (Reproduced with permission from: Novak V, Christiforidis G: Clinical promise. In: Robitaille PM, Berliner LJ, editors. Ultra high field magnetic resonance imaging (UHFMRI): Theory and applications, biological magnetic resonance. A series of contemporary topics and reviews. (With permission from: Novak V. Clinical Promise: Clinical Imaging at Ultra High Field. 2007; 26(13): 411–437) [77].



**Figure 3.**

A conceptual model of pathways that link cardiovascular risk factors (obesity, insulin resistance, chronic hyperglycemia and hypertension) with metabolic and autonomic dysregulation of arterial pressure and glucose, leading to increased oxidative stress and vascular inflammation. Their additive effects alter neurovascular coupling and vasoreactivity, leading to brain atrophy and functional decline.



**Figure 4.** Anatomical images of a diabetic (A1–A5) and a control subject (B1–B5) demonstrate that type 2 diabetes is associated with atrophy of gray (GM) and white matter (WM), enlarged ventricles) and diffuse periventricular hyperintensities (WMHs). 3D Magnetization prepared rapid gradient echo (MP\_RAGE) and fluid attenuated inversion recovery (FLAIR) images were acquired at 3 Tesla MRI (MP\_RAGE:  $T_R/T_E/T_I = 7.8/3.1/600$  ms, 3.0 mm slice thickness, 52 slices, bandwidth = 122 Hz per pixel, flip angle =  $10^\circ$ , 24 cm  $\times$  24 cm FOV, 256  $\times$  192 matrix size), FLAIR ( $T_R/T_E/T_I = 11000/161/2250$  ms, 5 mm slice thickness, 30 slices, bandwidth = 122 Hz per pixel, flip angle =  $90^\circ$ , 24 cm  $\times$  24 cm FOV, 256  $\times$  160 matrix size).