

Hypertension: A Harbinger of Stroke and Dementia Giuseppe Faraco and Costantino Iadecola

Hypertension. 2013;62:810-817; originally published online August 26, 2013;
doi: 10.1161/HYPERTENSIONAHA.113.01063

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:

<http://hyper.ahajournals.org/content/62/5/810>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Hypertension* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Hypertension* is online at:
<http://hyper.ahajournals.org/subscriptions/>

Hypertension A Harbinger of Stroke and Dementia

Giuseppe Faraco, Costantino Iadecola

Despite remarkable successes in prevention and treatment, hypertension (HTN) remains a major cause of morbidity and mortality worldwide.¹ The brain is one of the preeminent target organs in which high blood pressure is particularly damaging, contributing significantly to its burden of disease.¹ HTN is the biggest risk factor for stroke, the second cause of death worldwide and a major cause of long-term disability.² HTN is also a leading risk factor for vascular cognitive impairment (VCI),³ as well as Alzheimer disease (AD), the most common cause of dementia in the elderly.³ Therefore, HTN is involved in the pathogenesis of 2 major brain diseases: stroke and dementia. In this brief review, we first examine the role of HTN in the alterations in cerebrovascular structure and function underlying the pathological effects of HTN on the brain. Then, we examine the pathophysiological bases of these alterations, focusing on how high blood pressure promotes stroke and cognitive impairment. Finally, we discuss the impact of preventive and therapeutic approaches to mitigate the deleterious effects of HTN on the brain.

Alterations in Cerebrovascular Structure Induced by HTN

Adaptive Changes: Hypertrophy and Remodeling

Sustained elevations in blood pressure have profound effects on the structure of cerebral blood vessels, inducing adaptive changes aimed at reducing the mechanical stress on the arterial wall and protecting microvessels from pulsatile stress.⁴ In hypertrophic remodeling, the media thickens to encroach into the lumen, resulting in increased media cross-sectional area and media/lumen ratio (Figure 1). The size of vascular smooth muscle cells increases, and there is accumulation of extracellular matrix proteins, such as collagen and fibronectin, in the vessel wall.⁵ In eutrophic remodeling, smooth muscle cells undergo a rearrangement that leads to a reduction in the outer and inner diameters, whereas media/lumen ratio is increased and cross-sectional area is unaltered (Figure 1). In this case, the change in vascular smooth muscle cells size is negligible, and the reduction in lumen is attributable to a reorganization of cellular and acellular material in the vascular wall, accompanied by enhanced apoptosis in the outer regions of the blood vessel.⁵ Remodeling is damaging because it reduces the vessels' lumen and increases vascular resistance, and has

emerged as a potential risk factor for cardiovascular events and cerebrovascular disease.⁶

Longstanding HTN induces deposition of collagen and fibronectin and elastin fragmentation, leading to an increase in the stiffness of the wall of large arteries. Arterial stiffening is a good predictor of stroke and cognitive decline, and is associated with clinically silent brain lesions in patients with hypertension.^{3,7}

Atherosclerosis and Small Vessel Disease

HTN is a leading risk factor for atherosclerosis. A 10-mmHg increase in arterial pressure increases by 43% the odds of complex aortic atherosclerosis (protruding atheroma, ulcerated plaques, mobiles debris), highly predictive of ischemic strokes.⁸ Atherosclerotic lesions are also observed at sites of turbulent flow, such as the carotid bifurcation and the vertebrobasilar system, and less frequently in intracranial arteries (Figure 2). A potential mechanism is related to vascular shear stress at those sites leading to expression of innate immunity receptors on macrophages/monocytes and inflammation.⁹ Atherosclerotic plaques can cause stroke by releasing fragments and leading to artery-to-artery embolism, or by rupture and hemorrhage, resulting in acute cerebrovascular occlusions (Figure 2).

HTN also promotes highly distinctive alterations in small arteries and arterioles supplying the deep hemispheric white matter and basal ganglia, resulting in a condition known as small vessel disease (SVD; Figure 2). The susceptibility of these vessels to SVD may be related to their short linear path from larger vessels at the base of the brain, rendering them more vulnerable to the mechanical stresses imposed by HTN.¹⁰ The most common pathological substrates of SVD related to HTN is arteriolosclerosis.¹¹ The pathological features of arteriolosclerosis include loss of smooth muscle cells from the tunica media, deposits of fibro-hyaline material, narrowing of the lumen, and thickening of the vessel wall (lipohyalinosis¹¹; Figures 1 and 2). In more advanced lesions, fibrinoid necrosis of the vessel wall facilitates the rupture of the vessel resulting in microscopic hemorrhages or large hemorrhages typically in basal ganglia or thalamus (Figure 2). In addition, HTN induced capillary rarefaction, which may also contribute to the associated brain lesions in the periventricular white matter.

Received July 17, 2013; first decision July 22, 2013; revision accepted August 2, 2013.

From the Brain and Mind Research Institute, Weill Cornell Medical College, New York, NY.

Correspondence to Costantino Iadecola, Brain and Mind Research Institute, Weill Cornell Medical College, 407 E 61st St, RR-303, New York, NY 10065. E-mail coi2001@med.cornell.edu

(*Hypertension*. 2013;62:810-817.)

© 2013 American Heart Association, Inc.

Hypertension is available at <http://hyper.ahajournals.org>

DOI: 10.1161/HYPERTENSIONAHA.113.01063

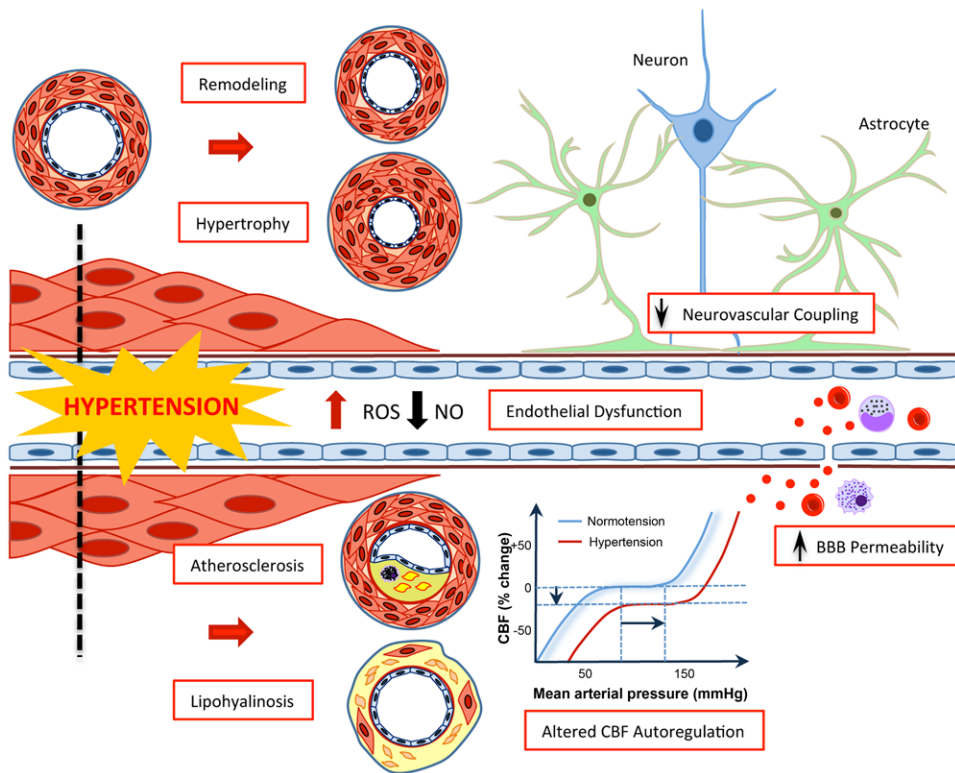


Figure 1. Effect of hypertension (HTN) on cerebral blood vessels. HTN induces profound alterations of critical regulatory mechanisms of the cerebral circulation, which, in concert with the structural alterations, compromise the blood supply to the brain and increase the risk for stroke and dementia. BBB indicates blood–brain barrier; CBF, cerebral blood flow; and ROS, reactive oxygen species.

Alterations in Cerebrovascular Function Induced by HTN

The brain is highly dependent on an adequate delivery of oxygen and glucose from the circulation, and cerebral blood flow (CBF) reductions impair neuronal function and, if protracted, induce brain damage.¹² Consequently, cerebrovascular control mechanisms assure that the delivery of oxygen and glucose is well matched to the energy demands of the cellular constituents of the brain. HTN induces profound alterations of these regulatory mechanisms, which, in concert with the structural changes described above, compromise the blood supply to the

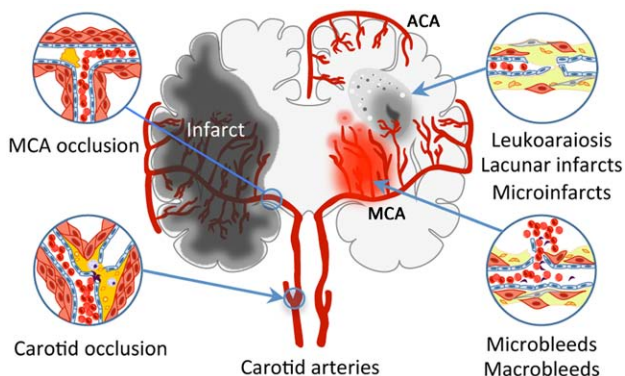


Figure 2. Ischemic brain lesions associated with hypertension (HTN). HTN induces atherosclerosis of major extracranial and intracranial arteries, which could lead to major infarcts. HTN causes both microbleeds and macrobleeds and is the main pathogenetic factor for small vessel disease responsible for lacunar infarcts, white matter lesions (leukoaraiosis), and microinfarcts. The subcortical white matter at the boundary between different vascular territories (middle cerebral artery [MCA] and anterior cerebral artery [ACA]) is particularly susceptible to damage.

brain. Next, we examine the major mechanisms regulating the cerebral circulation and their perturbation by HTN.

Cerebrovascular Autoregulation

Cerebrovascular autoregulation buffers the cerebrovascular effects of the wide fluctuations in arterial pressure that occur during the activities of daily living. Autoregulation allows the brain to maintain a steady blood flow between 60 and 150 mmHg of mean arterial pressure.¹³ Within this range, blood pressure increases result in constriction, and blood pressure decreases result in dilatation of cerebral resistance vessels, maintaining CBF relatively constant. Cerebral autoregulation depends on the intrinsic ability of vascular smooth muscle cells to constrict when transmural pressure increases (myogenic tone). Myogenic tone depends on the concerted action of ion channels on the vascular smooth muscle cells membrane, as well as stretch activated receptors, resulting in increases in intracellular Ca²⁺ or increases in the Ca²⁺ sensitivity of the contractile apparatus, ultimately leading to phosphorylation of contractile proteins and constriction.¹³

Regulation by Endothelial Cells

Cerebral endothelial cells have powerful effects on vascular tone and regulate CBF by releasing vasodilators (NO, prostacyclin, bradykinin, etc) and vasoconstrictors (endothelin-1 [ET-1], endothelium-derived constrictor factor, etc).¹⁴ Endothelium-derived vasoactive factors participate in the maintenance of resting CBF and may play a role in coordinating the vasodilatation of intraparenchymal arterioles with that of upstream pial arteries, and in local adjustments of flow in response to mechanical forces.¹² Another important aspect of endothelial cell function is the regulation of the blood–brain barrier (BBB).

Cerebral endothelial cells have a low vesicular transport and are linked to each other by tight junctions, which prevent the entry of hydrophilic substances into the brain.¹⁵ Specialized transport proteins on the endothelial cell membrane regulate the bidirectional transfer of substances into and from the brain parenchyma.¹⁵ The integrity of the BBB is vitally important to maintain the homeostasis of the cerebral microenvironments, which is a prerequisite for normal brain function.

Functional Hyperemia

Functional hyperemia is a homeostatic mechanism by which the vascular delivery of oxygen and glucose and the removal of metabolites produced by brain activity are coupled to the energy requirements of neurons and glia.¹² Therefore, CBF is dynamically related to the level of neural activity of the different brain regions. A growing body of evidence indicates that neurons, glia, and cerebrovascular cells, acting as an integrated unit, mediate the increase in CBF produced by neural activity.^{12,16} Neural activity induces the release of vasoactive mediators such as NO, prostanoids, carbon monoxide, cytochrome p450 metabolites, H⁺, and K⁺ ions that act at different levels of the cerebral vasculature to mediate the hemodynamic changes underlying the CBF increase.¹² Vasodilation of arterioles at the site of activation is accompanied by vasodilation of upstream pial arteries that supply the activated area, and this coordinated response is essential for increasing CBF efficiently.¹²

HTN and Cerebrovascular Dysfunction

HTN has profound effects on all aspects of the regulation of CBF (Figure 1). HTN alters cerebrovascular autoregulation, leading to a shift of the pressure–flow relationship to the right, such that higher pressures are needed to maintain the same level of cerebral perfusion (Figure 1). The lateral shift may be also associated with a reduction in resting CBF, resulting in a downward displacement of the curve¹⁷ (Figure 1). These alterations reduce cerebral perfusion at each level of blood pressure, compromising the ability of the brain to maintain adequate CBF in the face of hypotension or arterial occlusion. The mechanisms of the effects of HTN on autoregulation are not completely understood, but are likely to include a combination of effects on myogenic tone and on the changes in the mechanical characteristics of cerebral blood vessels induced by remodeling and stiffening.^{4,13} These changes in autoregulation are particularly damaging to the periventricular white matter, which is located at the boundary between different arterial territories¹⁸ and, as such, is most susceptible to hypoperfusion (Figure 2). Accordingly, the magnitude of autoregulatory dysfunction induced by HTN correlates with the severity of periventricular white matter injury.¹⁹ The HTN-induced autoregulatory impairment also leads to more severe brain damage after arterial occlusion in stroke models, which may underlie the increased susceptibility to large artery stroke.

HTN also alters functional hyperemia and endothelial function. Attenuations in cerebrovascular responses to endothelium-dependent vasodilators have been reported in rodent models of chronic HTN.^{20–22} Similarly, functional hyperemia, produced in the somatosensory cortex by activation of the facial whiskers, is attenuated in mice treated with slow-pressor doses of angiotensin II (Ang II) and in spontaneously

hypertensive rats.^{22,23} The cerebrovascular dysfunction precedes the HTN induced by slow-pressor Ang II infusion and persists beyond the elevation in blood pressure at the end of the infusion.²¹ Furthermore, doses of Ang II that do not elevate blood pressure produce cerebrovascular alterations comparable with those observed with slow-pressor or pressor doses,^{21,24,25} suggesting that the cerebrovascular actions of Ang II are independent of the elevation in blood pressure.

Consistent with findings in animal models, the increase in CBF induced by brain activation is attenuated in patients with chronic HTN, and the cerebrovascular dysfunction correlates with cognitive deficits.²⁶ Furthermore, the increase in retinal blood flow produced by light flickering, a model of function hyperemia, is blunted in individuals with hypertension.²⁷ Direct evidence of altered cerebrovascular endothelial responses in humans with HTN is lacking. But the NO synthase inhibitor L-NAME (*N*^G-nitro-L-arginine methyl ester) does not reduce retinal blood flow in patients with HTN, a finding consistent with NO-dependent endothelial dysfunction.²⁷ These observations, collectively, indicate that HTN disrupts key cerebrovascular control mechanisms aimed at maintaining the energy homeostasis of the brain, which act in concert with the structural alterations of cerebral blood vessels described earlier to produce brain dysfunction and damage.

Key Role of Oxidative Stress in the Cerebrovascular Effects of HTN

Several lines of evidence suggest that reactive oxygen species (ROS) are key mediators of the cerebrovascular damage produced by HTN. HTN promotes ROS production in cerebral blood vessels and ROS scavenger counteracts the effects of HTN on functional hyperemia and endothelial dysfunction, including alterations of the BBB.^{21,24,25,28} In models of Ang II HTN, ROS production is elevated in brain regions regulating cardiovascular function.²² Suppression of ROS in one of these regions, the subformal organ, prevents the alterations in functional hyperemia and endothelium-dependent responses induced by slow-pressor administration of Ang II.²² In this model, the cerebrovascular dysfunction involves, in addition to direct vascular effects of circulating Ang II, also activation of neurohumoral mechanisms leading to vasopressin release and upregulation of ET-1 in cerebral blood vessels.²² ET-1, in turn, leads to vascular ROS production through activation of ET type A receptors.²² In contrast, the cerebrovascular alterations induced by acute administration of pressor Ang II doses are entirely dependent on a direct action of Ang II on cerebral blood vessels leading to oxidative and nitrosative stress.^{24,25} Cerebrovascular ET-1, via ET type A receptor and ROS, is also involved in the cerebrovascular effects of the HTN induced by chronic intermittent hypoxia, a model of obstructive sleep apnea.²⁹ Oxidative stress has also been implicated in other vascular effects of HTN including vascular remodeling and inflammation.³⁰ The evidence for a role of ROS in the white matter damage produced by SVD is suggestive but limited. Increased markers of oxidative stress have been described in white matter lesions in autopsy studies.³¹ Furthermore, reduced circulating levels of NO metabolites, possibly reflecting increased oxidative stress, have been reported in patients with white matter lesions detected by MRI.³² More studies are clearly needed.

Among the potential sources of ROS in cerebral blood vessels,⁶ the enzyme nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase has emerged as a major contributor in the cerebrovascular effects of HTN.³³ Importantly, cerebral blood vessels have a greater capacity to produce NADPH oxidase-derived ROS than systemic vessels.³⁴ The cerebrovascular dysfunction induced by Ang II is not observed in mice lacking Nox2, and NADPH inhibition abrogates the alterations in endothelium-dependent vasodilation and functional hyperemia induced by Ang II.^{24,25} Nox2-derived radicals are also involved in the cerebrovascular remodeling induced by Ang II HTN.³⁰

Brain Lesions Underlying VCI

VCI includes a wide spectrum of cognitive alterations caused by cerebrovascular factors, ranging from mild cognitive impairment affecting a single cognitive domain, such as executive function, to full blown vascular dementia affecting multiple domains and impairing the activities of daily living.³ Stroke is a major cause of cognitive impairment. Up to one third of patients with stroke have cognitive impairment within 3 months, and having a stroke doubles the risk of dementia (poststroke dementia).³ Furthermore, the risk of VCI is increased in patients with no history of stroke in which imaging shows brain infarcts (silent infarcts).³ A single stroke affecting a region important for cognition, like the thalamus or the frontal lobe, can lead to cognitive impairment (strategic-infarct dementia).³ VCI and dementia can also result from multiple strokes destroying large amounts of brain tissue (multi-infarct dementia).³ However, SVD remains a major cause of VCI contributing up to 45% of dementia cases.³ Next, we examine the neuropathological alterations caused by cerebral SVD that have been linked to VCI.

Lacunar Infarcts

Lacunar infarcts, small (<20 mm in diameter) rounded lesion most commonly found in the basal ganglia, are commonly associated with SVD and are a strong predictor of VCI.³⁵ They have been attributed to acute occlusion of small perforating cerebral arteries (40–200 μ m diameter) because of SVD pathology or, less likely, embolism from upstream vessels.³⁶ More recently, evidence of white matter BBB disruption has been provided in patients with lacunes, raising the possibility that BBB alterations are early pathogenic events that could lead to secondary ischemia and inflammation.³⁶ Therefore, multiple factors are likely to be involved in the pathogenesis of lacunar infarcts.

Diffuse White Matter Damage

Another manifestation of SVD is diffuse white matter damage or leukoariosis, indicating a reduction in white matter density.^{3,11} High systolic blood pressure precedes the development of leukoariosis, and blood pressure lowering slows down its progression.³⁷ Often present in the periventricular white matter, leukoariosis could result from hypoxia-hypoperfusion. The periventricular white matter is thought to be more susceptible to hypoperfusion because it is located at the boundary between separate arterial territories¹⁸ (Figure 2). Supporting this hypothesis, CBF is reduced in normal

appearing periventricular white matter of patients with leukoariosis,³⁸ and hypoxia inducible genes are expressed in white matter lesions.³⁹ Endothelial dysfunction and BBB alterations produced by HTN could cause leakage of plasma proteins, leading to oxidative stress, inflammation, and edema, which compresses the tissue and contributes to hypoperfusion and demyelination.³⁶ Hypoxia could induce production of metalloproteases in oligodendrocyte precursors contributing to the BBB opening.^{31,40,41}

Microinfarcts

SVD is also associated with ischemic lesions not visible to the naked eyes (microinfarcts).⁴² Cerebral microinfarcts are small infarcts (<1 mm diameter) thought to be very common in the elderly, although their detection in vivo is challenging because of their small size.⁴² It is estimated that 1 or 2 microinfarcts in routine postmortem examination suggest the presence of hundreds of microinfarcts throughout the brain.⁴³ Microinfarcts are common in patients with vascular or mixed dementia but are an independent predictor of VCI.⁴² Number and the location of the microinfarcts are major determinants of cognitive dysfunction, the cortical location being more closely associated with dementia.⁴²

Cerebral Microbleeds and Macrobleeds

SVD also produces hemorrhagic manifestations. Cerebral microbleeds are small perivascular hemorrhages (2–10 mm) that can be detected histologically at autopsy or in vivo using iron-sensitive MRI sequences.⁴⁴ Microbleeds, which are observed in 10% to 20% of the elderly often in association with other SVD pathologies, are an independent predictor of cognitive decline.⁴⁴ HTN is a major risk factor of microbleeds, which in this condition are typically located in the basal ganglia, thalamus, brain stem, and cerebellum.⁴⁵ Microbleeds are frequently associated also with cerebral amyloid angiopathy, but in this case they tend to have a lobar distribution.⁴⁴ HTN is well known to cause large cerebral hemorrhages, typically in the basal ganglia or thalamus (Figure 2). The relationship between microbleeds and cerebral hemorrhages is not entirely clear, but microbleeds are associated with an increased risk of brain hemorrhage.⁴⁶

HTN and AD

AD and VCI are, respectively, the first and second most common causes of dementia in the elderly.³ Although traditionally considered separate pathologies, increasing evidence indicates that AD and VCI share common pathogenetic mechanisms.¹⁶ Vascular risk factors, such as HTN, smoking, hyperlipidemia, and diabetes mellitus, are also risk factors for AD.¹⁶ In particular, midlife HTN doubles the risk of AD later in life and accelerates the progression of the dementia.⁴⁷ Up to 50% of cases of dementia have mixed pathology featuring both vascular (SVD) and neurodegenerative lesions (amyloid plaques and neurofibrillary tangles).⁴⁸ Several studies have shown that HTN-induced lesions and AD may have an additive or synergistic effect and produce a more severe cognitive impairment than either process alone.¹⁶

Several postmortem studies have also reported more atherosclerosis in cerebral vessels of AD patients compared with

nondemented controls, a finding associated with increased amyloid plaques and neurofibrillary tangles.^{49,50} Furthermore, an increased amount of amyloid plaques and neurofibrillary tangles have been reported in the brain of patients with hypertension.⁵¹ β -amyloid ($A\beta$), a peptide involved in the pathogenesis of AD, is elevated in the blood of patients with VCI and could potentially contribute to vascular insufficiency and white matter injury.^{52,53} Furthermore, increases in diastolic blood pressure in midlife are linked to an increase in AD risk and to a reduction in plasma $A\beta$ decades later,⁵⁴ suggesting that the vascular dysfunction induced by HTN may inhibit the vascular transport of brain $A\beta$ into the plasma. HTN interacts with Apo ϵ 4 to promote amyloid deposition in healthy individuals, suggesting an interaction between vascular and genetic factors in increasing the susceptibility to AD.⁵¹ Patients with HTN and elevated AD biomarkers have increased gray matter atrophy, indicating that HTN may exacerbate gray matter damage in AD.⁵⁵

Experimental studies also support an interaction between HTN and $A\beta$. In mouse models of AD, $A\beta$ attenuates functional hyperemia and endothelium-dependent vasodilatation through mechanisms involving Nox2-derived ROS.^{56–58} However, unlike Ang II, the vascular effects of $A\beta$ require the scavenger receptor and $A\beta$ receptor CD36.⁵⁹ It is conceivable that HTN and $A\beta$ have an additive or synergistic pathogenic effect on cerebrovascular function. Consistent with this hypothesis, brain deposition of $A\beta$ is increased in hypertensive mice,⁶⁰ an effect attributed to inhibition of the perivascular and transvascular clearance of $A\beta$ secondary to vascular dysfunction and damage (Figure 3). HTN may also facilitate the transfer of $A\beta$ from blood to brain through the receptor for advanced glycation products (RAGE).⁶¹ Cerebral hypoxia-ischemia, which can occur with HTN, can also facilitate β -secretase-mediated cleavage of $A\beta$ from its precursor protein and increases the brain $A\beta$ burden.^{62,63}

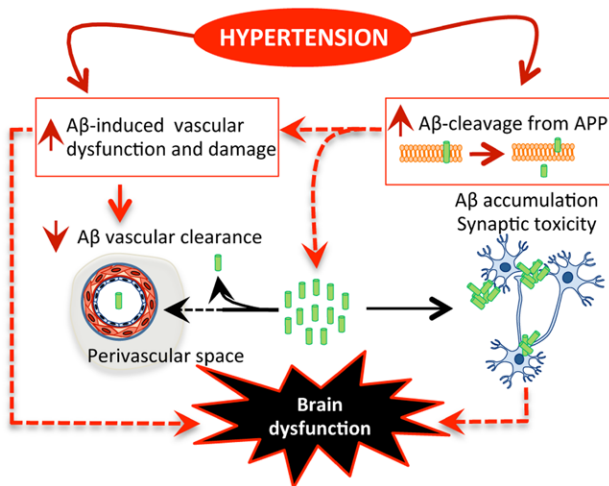


Figure 3. Interaction between hypertension (HTN) and Alzheimer disease. HTN increases the deposition of β -amyloid ($A\beta$) and might aggravate the cerebrovascular dysfunction induced by $A\beta$. HTN could impair the vascular clearance of $A\beta$ and increase its cleavage from the amyloid precursor protein (APP). Both of these effects would lead to increased $A\beta$ concentration in the brain parenchyma and blood vessels, aggravating the attendant vascular and synaptic dysfunction.

These observations, collectively, suggest that HTN may promote the development of AD through several mechanisms (Figure 3). First, HTN could impair the vascular clearance of the peptide, enhancing $A\beta$ accumulation in brain and vessels. Second, HTN could increase the cleavage of $A\beta$ from the amyloid precursor protein. Both of these effects would lead to increased $A\beta$ concentration in the brain parenchyma and blood vessels, aggravating the attendant vascular and synaptic dysfunction. Speculations aside, our understanding of human HTN and AD is far from complete and, consequently, the relationship between these 2 conditions is even less well understood. Nevertheless, because the pathological processes underlying AD starts decades before their clinical manifestation,⁶⁴ HTN is likely to exert its effects in the presymptomatic phase of the disease, stressing the need for early diagnosis and blood pressure lowering.

Treatment of HTN and Prevention of Stroke and Dementia

The National High Blood Pressure Education Program of the National Heart, Lung, and Blood Institute, introduced >40 years ago, has led to remarkable advances in the public awareness and treatment of HTN. This highly successful program is credited with a 70% to 80% reduction in the morbidity attributable to HTN, mainly heart attack and stroke.¹ The effect of HTN control on the incidence of stroke is indeed substantial, and for each 10-mmHg decrease in systolic blood pressure, there has been a one-third decrease in stroke risk.²

The effects of HTN treatment on VCI have been more difficult to assess,⁶⁵ and there is still a debate as to whether HTN control leads to a better cognitive outcome,^{10,65} except for the prevention of poststroke dementia.³ Some studies have shown a cognitive benefit from blood pressure lowering especially in the younger of the old, for example, Perindopril pROtection aGainst REcurrent Stroke (PROGRESS), Hypertension in the Very Elderly (HYVET), Systolic Hypertension in the Elderly (SHEP), Systolic Hypertension in Europe (SYST-EUR), whereas other studies have not, for example, Study on Cognition and Prognosis in the Elderly (SCOPE), Action in Diabetes and Vascular Disease (ADVANCE), and Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS).^{10,65} No specific class of antihypertensive agents has been consistently found to be more effective.³ Limitations of all these studies have been short follow-up, low rates of incident dementia, lack of accounting for cotreatments, and heterogeneity of the cognitive assessment, among others.^{3,65} Despite the controversy, a recent American Heart Association statement strongly recommends blood pressure lowering in patients who have suffered a stroke (Class I, level of evidence level B), and encourages treatment in the younger of the elderly (Class IIa, level of evidence B).³ The degree of blood pressure lowering remains uncertain, but there is evidence that more aggressive lowering may lead to a greater improvement in cerebral perfusion.¹⁷ The blood pressure threshold for starting treatment remains to be defined. Data from the Honolulu Heart Program/Honolulu Asian Aging Study suggest that 17% of late-life dementia cases are attributable to midlife systolic pressure levels between 120 and 140 mmHg.⁶⁶ Similarly, a progressive cognitive decline has been reported for blood

pressures between 120 and 140 mmHg,⁶⁷ arguing for starting treatment at prehypertensive blood pressure levels.

Treatments targeting oxidative stress have long been considered to treat HTN and related complications,⁶⁸ but it has been difficult to develop agents that cross the BBB and effectively reduce oxidative stress in brain.⁶⁹ Similarly, epidemiological studies have not shown a beneficial impact of dietary antioxidants on late-life dementia.⁷⁰ NADPH oxidase inhibitors would be valuable, and there is great interest in developing agents that could be used for cardiovascular and brain diseases.⁶⁹ On the other hand, the link between HTN and AD provides clues to potential therapeutic interventions that could benefit both diseases. Calcium-channel antagonists and inhibitors of the renin-angiotensin system increase A β removal from the brain and protect against cognitive dysfunction in mouse models.^{71,72} The renin-angiotensin system has been of particular interest in light of the observation that angiotensin-converting enzyme activity is increased in patients with AD, and that this enzyme may degrade A β , but there are many unresolved issues.⁷² Nevertheless, these preclinical observations raise the possibility of using specific blood pressure-lowering agents in patients with HTN at risk for AD. Furthermore, dietary interventions and exercise have been shown to be promising, and would also be valuable as a primary or adjuvant therapeutic approach.⁷³

Conclusions

The evidence reviewed in this article indicates that HTN, despite resounding successes in controlling its impact on morbidity and mortality, remains one of most pervasive and devastating diseases with broad consequences for worldwide health. HTN has profound effects on the brain and contributes in a substantive manner to stroke and dementia, highly prevalent diseases projected to have an even greater public health impact in decades to come because of population aging. Large and small cerebral vessels are key targets of HTN, resulting in pathological alteration of the vascular wall, impairment of vital hemodynamic responses regulating cerebral perfusion, and disruption of BBB permeability leading to major alterations in the brain microenvironment. Although oxidative stress and inflammation are important factors in the pathogenesis of these events, the cellular and molecular bases of the susceptibility of the white matter to HTN and other cerebrovascular risk factors have not been fully elucidated and represent a fruitful area of future research. The vascular changes induced by HTN not only increase the susceptibility of the brain to ischemic-hypoxic damage in vulnerable white matter regions but also promote the expression of AD neuropathology. The realization that HTN has an impact on AD represents a major departure from traditional views on the pathogenesis of AD, a disease in which vascular factors were thought not to play a role.¹⁶ However, our understanding of the interaction of HTN with AD is rudimentary at best, and much needs to be learned on the vascular biology of their respective effects on the cerebral vasculature and resulting cognitive impact. Although current approaches to treat HTN have dramatically reduced stroke incidence and mortality, the role of blood pressure control in the prevention of late-life dementia has been more difficult to assess. Questions remain on the blood pressure threshold for therapy initiation, length of treatment, and the blood pressure

reduction needed to maximize benefits and reduce risks. Whatever the impact on cognition, however, the great benefits for general health afforded by blood pressure control justify early and aggressive intervention. Nonpharmacological strategies based on diet and exercise may be particularly valuable in younger patients facing treatment for a lifetime.

Sources of Funding

The work was supported by National Institutes of Health grant HL96571 and Alzheimer's Association grant ZEN-11-202707.

Disclosures

None.

References

- Moser M, Roccella EJ. The treatment of hypertension: a remarkable success story. *J Clin Hypertens (Greenwich)*. 2013;15:88–91.
- Lawes CM, Bennett DA, Feigin VL, Rodgers A. Blood pressure and stroke: an overview of published reviews. *Stroke*. 2004;35:1024.
- Gorelick PB, Scuteri A, Black SE, et al; American Heart Association Stroke Council, Council on Epidemiology and Prevention, Council on Cardiovascular Nursing, Council on Cardiovascular Radiology and Intervention, and Council on Cardiovascular Surgery and Anesthesia. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42:2672–2713.
- Scuteri A, Nilsson PM, Tzourio C, Redon J, Laurent S. Microvascular brain damage with aging and hypertension: pathophysiological consideration and clinical implications. *J Hypertens*. 2011;29:1469–1477.
- Mulvany MJ. Small artery remodelling in hypertension. *Basic Clin Pharmacol Toxicol*. 2012;110:49–55.
- Faraci FM. Protecting against vascular disease in brain. *Am J Physiol Heart Circ Physiol*. 2011;300:H1566–H1582.
- Henskens LH, Kroon AA, van Oostenbrugge RJ, Gronenschild EH, Fuss-Lejeune MM, Hofman PA, Lodder J, de Leeuw PW. Increased aortic pulse wave velocity is associated with silent cerebral small-vessel disease in hypertensive patients. *Hypertension*. 2008;52:1120–1126.
- 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.
- Sakamoto H, Aikawa M, Hill CC, Weiss D, Taylor WR, Libby P, Lee RT. Biomechanical strain induces class a scavenger receptor expression in human monocyte/macrophages and THP-1 cells: a potential mechanism of increased atherosclerosis in hypertension. *Circulation*. 2001;104:109–114.
- Sörös P, Whitehead S, Spence JD, Hachinski V. Antihypertensive treatment can prevent stroke and cognitive decline. *Nat Rev Neurol*. 2013;9:174–178.
- Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol*. 2010;9:689–701.
- Iadecola C. Neurovascular regulation in the normal brain and in Alzheimer's disease. *Nat Rev Neurosci*. 2004;5:347–360.
- Cipolla MJ. *The Cerebral Circulation*. San Rafael, CA: Morgan & Claypool Life Sciences; 2009.
- Andresen J, Shafi NI, Bryan RM Jr. Endothelial influences on cerebrovascular tone. *J Appl Physiol*. 2006;100:318–327.
- Neuwelt EA, Bauer B, Fahlke C, Fricker G, Iadecola C, Janigro D, Leybaert L, Molnár Z, O'Donnell ME, Povlishock JT, Saunders NR, Sharp F, Stanimirovic D, Watts RJ, Drewes LR. Engaging neuroscience to advance translational research in brain barrier biology. *Nat Rev Neurosci*. 2011;12:169–182.
- Iadecola C. The overlap between neurodegenerative and vascular factors in the pathogenesis of dementia. *Acta Neuropathol*. 2010;120:287–296.
- Tryambake D, He J, Firbank MJ, O'Brien JT, Blamire AM, Ford GA. Intensive blood pressure lowering increases cerebral blood flow in older subjects with hypertension. *Hypertension*. 2013;61:1309–1315.
- De Reuck J. The human periventricular arterial blood supply and the anatomy of cerebral infarctions. *Eur Neurol*. 1971;5:321–334.
- Matsushita K, Kuriyama Y, Nagatsuka K, Nakamura M, Sawada T, Omae T. Periventricular white matter lucency and cerebral blood flow autoregulation in hypertensive patients. *Hypertension*. 1994;23:565–568.

20. Didion SP, Sigmund CD, Faraci FM. Impaired endothelial function in transgenic mice expressing both human renin and human angiotensinogen. *Stroke*. 2000;31:760–764; discussion 765.
21. 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.
22. 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.
23. Calcinaghi N, Wyss MT, Jolivet R, Singh A, Keller AL, Winnik S, Fritschy JM, Buck A, Matter CM, Weber B. Multimodal imaging in rats reveals impaired neurovascular coupling in sustained hypertension. *Stroke*. 2013;44:1957–1964.
24. 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.
25. Girouard H, Park L, Anrather J, Zhou P, Iadecola C. Angiotensin II attenuates endothelium-dependent responses in the cerebral microcirculation through nox-2-derived radicals. *Arterioscler Thromb Vasc Biol*. 2006;26:826–832.
26. 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.
27. 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.
28. Zhang M, Mao Y, Ramirez SH, Tuma RF, Chabrashvili T. Angiotensin II induced cerebral microvascular inflammation and increased blood-brain barrier permeability via oxidative stress. *Neuroscience*. 2010;171:852–858.
29. Capone C, Faraco G, Coleman C, Young CN, Pickel VM, Anrather J, Davisson RL, Iadecola C. Endothelin 1-dependent neurovascular dysfunction in chronic intermittent hypoxia. *Hypertension*. 2012;60:106–113.
30. De Silva TM, Faraci FM. Effects of angiotensin II on the cerebral circulation: role of oxidative stress. *Front Physiol*. 2012;3:484.
31. Back SA, Kroenke CD, Sherman LS, Lawrence G, Gong X, Taber EN, Sonnen JA, Larson EB, Montine TJ. White matter lesions defined by diffusion tensor imaging in older adults. *Ann Neurol*. 2011;70:465–476.
32. Shibata H, Nabika T, Moriyama H, Masuda J, Kobayashi S. Correlation of NO metabolites and 8-iso-prostaglandin F2a with periventricular hyperintensity severity. *Arterioscler Thromb Vasc Biol*. 2004;24:1659–1663.
33. Iadecola C, Davisson RL. Hypertension and cerebrovascular dysfunction. *Cell Metab*. 2008;7:476–484.
34. Miller AA, Drummond GR, Schmidt HH, Sobey CG. NADPH oxidase activity and function are profoundly greater in cerebral versus systemic arteries. *Circ Res*. 2005;97:1055–1062.
35. Jokinen H, Gouw AA, Madureira S, Ylikoski R, van Straaten EC, van der Flier WM, Barkhof F, Scheltens P, Fazekas F, Schmidt R, Verdellho A, Ferro JM, Pantoni L, Inzitari D, Erkinjuntti T; LADIS Study Group. Incident lacunes influence cognitive decline: the LADIS study. *Neurology*. 2011;76:1872–1878.
36. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. *Lancet Neurol*. 2013;12:483–497.
37. Verhaaren BF, Vernooij MW, de Boer R, Hofman A, Niessen WJ, van der Lugt A, Ikram MA. High blood pressure and cerebral white matter lesion progression in the general population. *Hypertension*. 2013;61:1354–1359.
38. O'Sullivan M, Lythgoe DJ, Pereira AC, Summers PE, Jarosz JM, Williams SC, Markus HS. Patterns of cerebral blood flow reduction in patients with ischemic leukoaraiosis. *Neurology*. 2002;59:321–326.
39. Fernando MS, Simpson JE, Matthews F, Brayne C, Lewis CE, Barber R, Kalaria RN, Forster G, Esteves F, Wharton SB, Shaw PJ, O'Brien JT, Ince PG; 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.
40. Seo JH, Miyamoto N, Hayakawa K, Pham LD, Maki T, Ayata C, Kim KW, Lo EH, Arai K. Oligodendrocyte precursors induce early blood-brain barrier opening after white matter injury. *J Clin Invest*. 2013;123:782–786.
41. Rosenberg GA. Matrix metalloproteinases and their multiple roles in neurodegenerative diseases. *Lancet Neurol*. 2009;8:205–216.
42. Smith EE, Schneider JA, Wardlaw JM, Greenberg SM. Cerebral microinfarcts: the invisible lesions. *Lancet Neurol*. 2012;11:272–282.
43. Westover MB, Bianchi MT, Yang C, Schneider JA, Greenberg SM. Estimating cerebral microinfarct burden from autopsy samples. *Neurology*. 2013;80:1365–1369.
44. Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Al-Shahi Salman R, Warach S, Launer LJ, Van Buchem MA, Breteler MM; Microbleed Study Group. Cerebral microbleeds: a guide to detection and interpretation. *Lancet Neurol*. 2009;8:165–174.
45. Fazekas F, Kleinert R, Roob G, Kleinert G, Kapeller P, Schmidt R, Hartung HP. Histopathologic analysis of foci of signal loss on gradient-echo T2*-weighted MR images in patients with spontaneous intracerebral hemorrhage: evidence of microangiopathy-related microbleeds. *AJNR Am J Neuroradiol*. 1999;20:637–642.
46. Greenberg SM, Eng JA, Ning M, Smith EE, Rosand J. Hemorrhage burden predicts recurrent intracerebral hemorrhage after lobar hemorrhage. *Stroke*. 2004;35:1415–1420.
47. Skoog I, Gustafson D. Update on hypertension and Alzheimer's disease. *Neurol Res*. 2006;28:605–611.
48. Schneider JA, Arvanitakis Z, Leurgans SE, Bennett DA. The neuropathology of probable Alzheimer disease and mild cognitive impairment. *Ann Neurol*. 2009;66:200–208.
49. Rohrer AE, Kuo YM, Esh C, Knebel C, Weiss N, Kalback W, Luehrs DC, Childress JL, Beach TG, Weller RO, Kokjohn TA. Cortical and leptomeningeal cerebrovascular amyloid and white matter pathology in Alzheimer's disease. *Mol Med*. 2003;9:112–122.
50. Yarchoan M, Xie SX, Kling MA, Toledo JB, Wolk DA, Lee EB, Van Deerlin V, Lee VM, Trojanowski JQ, Arnold SE. Cerebrovascular atherosclerosis correlates with Alzheimer pathology in neurodegenerative dementias. *Brain*. 2012;135(pt 12):3749–3756.
51. Rodrigue KM, Rieck JR, Kennedy KM, Devous MD Sr, Diaz-Arrastia R, Park DC. Risk factors for β -amyloid deposition in healthy aging: vascular and genetic effects. *JAMA Neurol*. 2013;70:600–606.
52. Gomis M, Sobrino T, Ois A, Millán M, Rodríguez-Campello A, Pérez de la Ossa N, Rodríguez-González R, Jiménez-Conde J, Cuadrado-Godia E, Roquer J, Dávalos A. Plasma beta-amyloid 1–40 is associated with the diffuse small vessel disease subtype. *Stroke*. 2009;40:3197–3201.
53. Park L, Zhou P, Koizumi K, El Jamal S, Previti ML, Van Nostrand WE, Carlson G, Iadecola C. Brain and circulating levels of A β 1–40 differentially contribute to vasomotor dysfunction in the mouse brain. *Stroke*. 2013;44:198–204.
54. Shah NS, Vidal JS, Masaki K, Petrovitch H, Ross GW, Tilley C, DeMattos RB, Tracy RP, White LR, Launer LJ. Midlife blood pressure, plasma β -amyloid, and the risk for Alzheimer disease: the Honolulu Asia Aging Study. *Hypertension*. 2012;59:780–786.
55. Glodzik L, Mosconi L, Tsui W, de Santi S, Zinkowski R, Pirraglia E, Rich KE, McHugh P, Li Y, Williams S, Ali F, Zetterberg H, Blennow K, Mehta P, de Leon MJ. Alzheimer's disease markers, hypertension, and gray matter damage in normal elderly. *Neurobiol Aging*. 2012;33:1215–1227.
56. Niwa K, Younkin L, Ebeling C, Turner SK, Westaway D, Younkin S, Ashe KH, Carlson GA, Iadecola C. Abeta 1–40-related reduction in functional hyperemia in mouse neocortex during somatosensory activation. *Proc Natl Acad Sci U S A*. 2000;97:9735–9740.
57. Iadecola C, Zhang F, Niwa K, Eckman C, Turner SK, Fischer E, Younkin S, Borchelt DR, Hsiao KK, Carlson GA. SOD1 rescues cerebral endothelial dysfunction in mice overexpressing amyloid precursor protein. *Nat Neurosci*. 1999;2:157–161.
58. Park L, Zhou P, Pistick R, Capone C, Anrather J, Norris EH, Younkin L, Younkin S, Carlson G, McEwen BS, Iadecola C. Nox2-derived radicals contribute to neurovascular and behavioral dysfunction in mice overexpressing the amyloid precursor protein. *Proc Natl Acad Sci U S A*. 2008;105:1347–1352.
59. Park L, Zhou J, Zhou P, Pistick R, El Jamal S, Younkin L, Pierce J, Arreguin A, Anrather J, Younkin SG, Carlson GA, McEwen BS, Iadecola C. Innate immunity receptor CD36 promotes cerebral amyloid angiopathy. *Proc Natl Acad Sci U S A*. 2013;110:3089–3094.
60. Gentile MT, Poulet R, Di Pardo A, Cifelli G, Maffei A, Vecchione C, Passarelli F, Landolfi A, Carullo P, Lembo G. Beta-amyloid deposition in brain is enhanced in mouse models of arterial hypertension. *Neurobiol Aging*. 2009;30:222–228.
61. 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.

62. Sun X, He G, Qing H, Zhou W, Dobie F, Cai F, Staufenbiel M, Huang LE, Song W. Hypoxia facilitates Alzheimer's disease pathogenesis by up-regulating BACE1 gene expression. *Proc Natl Acad Sci U S A*. 2006;103:18727–18732.
63. Tesco G, Koh YH, Kang EL, Cameron AN, Das S, Sena-Esteves M, Hiltunen M, Yang SH, Zhong Z, Shen Y, Simpkins JW, Tanzi RE. Depletion of GGA3 stabilizes BACE and enhances beta-secretase activity. *Neuron*. 2007;54:721–737.
64. Bateman RJ, Xiong C, Benzinger TL, et al; Dominantly Inherited Alzheimer Network. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med*. 2012;367:795–804.
65. Dichgans M, Zietemann V. Prevention of vascular cognitive impairment. *Stroke*. 2012;43:3137–3146.
66. Launer LJ, Hughes T, Yu B, Masaki K, Petrovitch H, Ross GW, White LR. Lowering midlife levels of systolic blood pressure as a public health strategy to reduce late-life dementia: perspective from the Honolulu Heart Program/Honolulu Asia Aging study. *Hypertension*. 2010;55:1352–1359.
67. Knecht S, Wersching H, Lohmann H, Bruchmann M, Duning T, Dziewas R, Berger K, Ringelstein EB. High-normal blood pressure is associated with poor cognitive performance. *Hypertension*. 2008;51:663–668.
68. Delles C, Miller WH, Dominiczak AF. Targeting reactive oxygen species in hypertension. *Antioxid Redox Signal*. 2008;10:1061–1077.
69. Drummond GR, Selemidis S, Griendling KK, Sobey CG. Combating oxidative stress in vascular disease: NADPH oxidases as therapeutic targets. *Nat Rev Drug Discov*. 2011;10:453–471.
70. Laurin D, Masaki KH, Foley DJ, White LR, Launer LJ. Midlife dietary intake of antioxidants and risk of late-life incident dementia: the Honolulu-Asia Aging study. *Am J Epidemiol*. 2004;159:959–967.
71. Paris D, Bachmeier C, Patel N, Quadros A, Volmar CH, Laporte V, Ganey J, Beaulieu-Abdelahad D, Ait-Ghezala G, Crawford F, Mullan MJ. Selective antihypertensive dihydropyridines lower A β accumulation by targeting both the production and the clearance of A β across the blood-brain barrier. *Mol Med*. 2011;17:149–162.
72. Kehoe PG, Miners S, Love S. Angiotensins in Alzheimer's disease—friend or foe? *Trends Neurosci*. 2009;32:619–628.
73. Smith PJ, Blumenthal JA, Babyak MA, Craighead L, Welsh-Bohmer KA, Browndyke JN, Strauman TA, Sherwood A. Effects of the dietary approaches to stop hypertension diet, exercise, and caloric restriction on neurocognition in overweight adults with high blood pressure. *Hypertension*. 2010;55:1331–1338.