Published in final edited form as:

J Am Soc Hypertens. 2014 August ; 8(8): 561–570. doi:10.1016/j.jash.2014.04.002.

The Impact of Hypertension on Cerebral Perfusion and Cortical Thickness in Older Adults

Michael L. Alosco, M.A.^A, John Gunstad, Ph.D.^A, Xiaomeng Xu, Ph.D.^B, Uraina S. Clark, Ph.D.^C, Donald R. Labbe, Ph.D.^D, Hannah H. Riskin-Jones, B.A.^E, Gretel Terrero, B.S.^F, Nicolette F. Schwarz, M.S.^G, Edward G. Walsh, Ph.D.^H, Athena Poppas, M.D.^I, Ronald A. Cohen, Ph.D.^J, and Lawrence H. Sweet, Ph.D.^{D,G}

^ADepartment of Psychology, Kent State University, Kent, OH, USA

^BDepartment of Psychology, Idaho State University, Pocatello, ID, USA

^CDepartment of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

^DAlpert Medical School of Brown University, the Department of Psychiatry and Human Behavior, Providence, RI, USA

^EBrain Behavior and Aging Research Center, VA Greater Los Angeles Healthcare System, Los Angeles, CA, USA

^FAlpert Medical School of Brown University, Providence, RI, USA

^GDepartment of Psychology, University of Georgia, Athens, GA, USA

^HBrown University, Departments of Neuroscience and Diagnostic Imaging, Providence, RI, USA

^IAlpert Medical School of Brown University, Department of Medicine, Providence, RI, USA

^JCognitive Aging and Memory Program, Clinical Translational Research Program, Institute on Aging, University of Florida, Gainesville, FL, USA

Abstract

Background—Hypertension may increase risk for dementia possibly because of its association with decreased cortical thickness. Disturbed cerebral autoregulation is one plausible mechanism by which hypertension impacts the cerebral structure, but the associations among hypertension, brain perfusion, and cortical thickness are poorly understood.

Methods—The current sample consisted of 58 older adults with varying levels of vascular disease. Diagnostic history of hypertension and antihypertensive medication status was ascertained through self-report and, when available, confirmed by medical record review. All participants

© 2014 American Society of Hypertension. Published by Elsevier Inc. All rights reserved.

Address Correspondence to: Michael Alosco, M.A., Department of Psychology, Kent State University, Kent OH USA 44242; Phone 203-417-1892; Fax 330-672-3786; Malosco@kent.edu.

There are no conflicts of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

underwent arterial spin labeling and T1-weighted magnetic resonance imaging (MRI) to quantify total and regional cortical perfusion and thickness.

Results—Analysis of covariance adjusting for medical variables showed that participants with hypertension exhibited reduced temporal and occipital brain perfusion as well as total and regional cortical thickness relative to those without hypertension. The effects of hypertension on total brain perfusion remained unchanged even after adjustment for age, though no such pattern emerged for cortical thickness. Decreased total brain perfusion predicted reduced thickness of the total brain as well as of the frontal, temporal, and parietal lobe cortices. Antihypertensive treatment was not associated with total cerebral perfusion or cortical thickness.

Discussion—This study provides initial evidence for the adverse effects of a diagnostic history of hypertension on brain hypoperfusion and reduced cortical thickness. Longitudinal studies are needed to investigate the role of hypertension and its interaction with other contributing factors (e.g., age) in the manifestation of cerebral hypoperfusion and reduced cortical thickness.

Keywords

Hypertension; cerebral perfusion; arterial spin labeling; cortical thickness

Introduction

Approximately 1 out of 3 U.S. adults has hypertension and nearly 50% of these individuals do not have it controlled.¹ This is concerning, as hypertension elevates mortality risk and leads to chronic medical conditions such as cardiovascular disease (CVD).¹ Hypertension is also associated with poor neurocognitive outcomes, including increased risk for Alzheimer's disease and vascular dementia.^{2,3} These adverse outcomes may in part be attributed to the negative impact of hypertension on the brain. Hypertension is linked with stroke, greater white matter hyperintensity (WMH) volume, and total and regional (e.g., hippocampus) brain atrophy.⁴⁻⁶ Although poorly understood, hypertension may also be associated with decreased cortical thickness—a sensitive risk factor for cognitive decline and Alzheimer's disease conversion.⁷⁻¹¹

Hypertension is associated with reduced cerebral blood flow, which in-turn, may serve as one possible etiology for adverse brain changes in hypertensive older adults. Specifically, hypertension may contribute to reduced cerebral blood flow to cortical and subcortical structures.^{12,13} Reduced brain perfusion has been correlated with decreased integrity of the cerebral structure, including decreased thickness of the cortex. Poorer cerebral circulation is linked with reduced cortical thickness in older adults, with specific effects found on frontal and temporal lobe cortices.¹⁴ Individuals susceptible to lower brain perfusion levels (e.g., Apolipoprotein E epsilon 4 carriers) also exhibit reduced thickness of regions vulnerable to aging (e.g., medial prefrontal cortex) and Alzheimer's disease (e.g., occipitotemporal and basal temporal cortices).^{8, 15-17}

The adverse effects of hypertension on the brain may be attenuated through medication therapy. Blood pressure lowering in older adults has been suggested to reduce the risk of stroke as well as the development of dementia.^{18,19} Antihypertensive treatment is associated

with better cerebral perfusion levels²⁰ and may also reduce risk of brain atrophy and lesions.²¹ Nonetheless, the effects of antihypertensive drugs on the brain appear to be complicated. As an example, past work also shows antihypertensive treatment has limited effects on the brain structure and does not reduce dementia risk.^{22,23} Even further, there is also extant evidence suggesting that antihypertensive medications may have no impact on cerebral perfusion levels.²⁴

As reviewed above, past studies have examined the effect of hypertension on cerebral blood flow and brain morphometry, yet, no study has simultaneously investigated the associations among hypertension, brain perfusion, and cortical thickness. The purpose of the current study was to examine the associations among hypertension, cerebral blood flow, and cortical thickness in a representative sample of older adults using T1-weighted magnetic resonance imaging (MRI) and arterial spin labeling, a perfusion MRI technique. We also examined whether antihypertensive treatment was associated with better cerebral perfusion and increased cortical thickness.

Methods

Participants

A total of 58 older adults were recruited from a larger National Institutes of Health study examining the effects of CVD on the brain. The present sample consisted of 58 participants with complete MRI, medical, and demographic data (see Table 1). Participants were recruited from outpatient cardiology offices and advertisements in local papers and screened for study eligibility. The inclusion criteria included English-speaking older men and women over the age of 50. Potential participants were excluded for significant neurological disease (e.g., history of stroke, multiple sclerosis), moderate or severe traumatic brain injury (with loss of consciousness), diagnosis of a current psychiatric illness, history of substance abuse with subsequent hospitalization, or any contraindications for MRI (e.g., some metal implants). The current sample size consisted of participants with perfusion data.

Measures

Acquisition of Arterial Spin Labeling (ASL) and T₁-Magnetization Prepared Rapid Acquisition GRE Data—All scans were performed using a 3 Tesla Siemens Tim Trio scanner with a 32 channel head receiver array and body resonator transmit coil located on the Brown University campus. Participants were placed head first in the supine position. Foam pads were placed in the space around the head to limit motion.

Following acquisition of a three-axis localizer scan, a 3D T₁-MPRAGE scan was acquired with 1mm isotropic resolution. This scan was acquired using parameters Repetition Time=1900ms, Echo Time=2.98ms, Inversion Time=900ms, and readout flip angle=9° to provide a 3D T₁ image dataset for grey-white matter segmentation used in the analysis of cortical thickness and for anatomical localization of the ASL images. ASL scans were acquired using a proximal inversion with control for off-resonance effects - Quantitative imaging of perfusion using a single subtraction, second version with thin-slice T11 periodic saturation technique.²⁵ For ASL scans, 71 pairs (control, perfusion weighted) of motion

corrected images were averaged to provide the mean difference image for perfusion map computation. The inversion labeling slab, 110mm in thickness, was placed with its proximal edge 12mm from the inferior boundary of the imaged region. Eighteen slices of 6mm thickness (in-plane voxel size 3mm²) were acquired over two scans (9 slices in the first scan, 9 slices in the second). Timing parameters were TR=2500ms, TI₁=700ms, TI₂=1800ms (inversion to start of the 64² echo planar image readout sequence with TE=16ms). Scan time for each ASL run was 4.5 minutes.

Quantification of Cortical Thickness—Morphometric data were quantified from the T1-weighted MPRAGE acquisition. These procedures are based on established techniques and procedures for surface and subcortical reconstruction using the FreeSurfer software package and have been described previously.^{26–30} The fully automated FreeSurfer v5.0 recon-all processing stream was completed for all participants. Briefly, T₁ volumes were normalized to the Montreal Neurological Institute geometry and segmented using standard T₁ gray, white, Cerebrospinal fluid, and non-brain templates using FreeSurfer reconstruction.^{26,27} This generated separate left and right cerebral hemisphere cortical ribbon masks and cortical parcellation using the Desikan-Killiany atlas for each participant. Left and right masks were combined to form the cortical ribbon mask. Results underwent quality control to confirm absence of any errors or defects in the segmentation.

Quantification of Perfusion—For a detailed description of methodology used to calculate the perfusion maps please refer to Alosco et al. (2013).¹⁴ Briefly, M₀ and M for each pixel were used to produce perfusion maps for each slice using Matlab (Math Works, Natick, MA). The M₀ map for each slice was the first image acquired in the dataset, which was acquired with the longitudinal magnetization at full equilibrium, without any inversion or saturation preparation. Perfusion maps were formed by averaging the 71 pairs of motion corrected M₀ and M maps. The tissue parameters^{31–33} used were T_{1a}=1664ms, T_{1T}=1300ms (grey matter) or 1000ms (white matter), T_{ex}=1000ms, and λ=0.9ml/g. Inversion efficiency (α) was set to 0.95 based on scanner manufacturer recommendation (α=1 corresponds to perfect inversion). Values of q=0.93 for grey matter and 0.85 for white matter were applied to the perfusion calculation by pixel based on the grey-white matter tissue segmentation. To accomplish this, Statistical Parametric Mapping 5 tissue segmentation^{34,35} was applied to the T₁-MPRAGE data, generating gray matter and white matter posterior probability maps for each participant in native space. The posterior probability maps were then thresholded using a minimum probability of 0.70, minimizing partial volume effects for each tissue type, yielding a binary gray matter mask and a binary white matter mask.

The whole brain geometry for each participant's mean perfusion data was established by concatenating the inferior 9 axial slice and superior 9 axial slice relative cerebral blood flow (CBF) maps. The FreeSurfer cortical ribbon, anatomically based cortical parcellation (Desikan-Killiany atlas), and binary segmentation masks were then aligned with and resampled to the same geometry as the perfusion data using Analysis of Functional NeuroImages/SUMA.³⁶ A whole brain perfusion map was then created using the following formula: Whole brain perfusion = (binary gray matter mask + binary white matter mask) ×

(perfusion data). Following alignment and resampling, the mean and standard deviation of all perfusion values between 1 and 100 were calculated for each region of interest (as outlined in the Desikan-Killiany atlas), the cortical ribbon, and the whole brain.

Physiological examination—Participants' weights and heights were measured and used to calculate Body Mass Index (BMI) using the standard formula: $(\text{mass in kg})/(\text{height in meters})^2$. A transthoracic echocardiogram was conducted with two-dimensional apical views from each participant according to standards of the American Society of Echocardiography.³⁷ Cardiac index was calculated by dividing cardiac output by BMI, which yielded a measure of cardiac output that controlled for body size.

Demographic and Medical Characteristics—The patient's medical history and currently prescribed medications were self-reported and confirmed by medical records when available. Medications were categorized by class and those identified as cardiovascular medications were reviewed and confirmed by a clinical cardiologist. Through these methods, physician diagnostic history (positive or negative diagnostic history) of hypertension as well as diabetes, atrial fibrillation, and elevated total cholesterol were ascertained. Currently prescribed antihypertensive medication (yes or no) was also ascertained. In accords with the American Heart Association guidelines, the following medications operationalized antihypertensive medication agents: diuretics, angiotensin-converting enzyme (ACE) inhibitor, calcium channel blockers, beta blockers, and angiotensin II receptor blockers (ARBs), and other antihypertensive agents.

Procedures

Institutional Review Board approval was granted and written informed consent was obtained from all participants prior to study enrollment. At an initial study visit, all participants completed medical self-report measures and a comprehensive medical record review was performed. At subsequent study visits, participants underwent a physiological examination as well as neuroimaging procedures.

Statistical Analyses

A series of calculations were performed to account for the variability in the size of each brain region that contributed to the computed lobar and total brain composites. Specifically, a total voxel count composite was computed for each lobe (i.e., frontal, temporal, parietal, and occipital) that consisted of the sum of the left and right hemisphere voxel counts of each brain structure that comprise their respective lobe. The proportion of the voxel count for each region to the total voxel count of its respective lobe was then calculated. The mean perfusion of left and right hemisphere individual brain regions was computed and, for each region, the cross product between the voxel count proportion value and the mean perfusion was determined. The same procedures were followed for cortical thickness. Frontal, temporal, parietal, and occipital lobe perfusion and thickness composites consisted of the sum of the size weighted brain structures that comprise their respective lobe.³⁸ A mean of all lobes was also performed to generate total brain perfusion and cortical thickness composites. Of note, due to individual differences in neuroanatomy there were cases in which some neuroanatomical structures were too small to generate a reliable perfusion value. For these

instances, the lobar composites were based on complete data of the remaining regions that comprise that lobe.

Analyses of Covariance (ANCOVA) were first performed to determine the effects of hypertension on total brain perfusion and perfusion to each lobe. Diagnostic history of hypertension served as the between subjects variable and the dependent variables included frontal, temporal, parietal, occipital, and total brain perfusion. Analyses were adjusted for cardiac index, and diagnostic history of diabetes, atrial fibrillation, and elevated total cholesterol in order to account for their prevalence and known and distinct effects on the brain and cardiac function in older adults. Chi-square analyses and independent samples *t*-tests also examined the associations among the covariates in order to examine the possibility of multicollinearity. These same procedures were performed to examine the effects of hypertension on total brain and lobar cortical thickness.

Partial correlations controlling for cardiac index, and diagnostic history of diabetes, atrial fibrillation, and elevated total cholesterol then examined the associations between total and regional cerebral perfusion with cortical thickness. Finally, using the above-described ANCOVA analyses we examined whether those participants prescribed an antihypertensive agent exhibited better total cerebral perfusion and increased cortical thickness than those not prescribed such medication. Because only one participant exhibited uncontrolled hypertension, analyses examining the effects of antihypertensive medications were conducted among the full sample (i.e., participants with and without a history of hypertension) rather than between untreated versus treated hypertension.

Given the critical role of age in the development of brain pathology, bivariate correlations examined the association between age and total brain perfusion and total cortical thickness, and if significant, analyses were repeated to determine older age as a possible confound. Because calculations were conducted to account for the size of each individual brain structure, gender and intracranial volume were not included as covariates in any of the above analyses.

Results

Sample Medical Characteristics

On average, the sample exhibited a cardiac index (mean (SD) = 2.77 (0.56) L/min/m²) that fell in the lower end of the normative range. Of the sample, 39.7% had a diagnostic history of hypertension and 51.7% of the sample was prescribed an antihypertensive agent. ACE inhibitors were most prevalent (27.6%) followed by beta blockers (25.9%); other antihypertensive agents (12.1%), calcium channel blockers (8.6%), diuretics (8.6%), and ARBs (1.7%) were less common.

Antihyperlipidemic medication was also prescribed in more than half of the sample. Indeed, cardiovascular disease and its risk factors were common in this sample, most notably coronary artery disease, atrial fibrillation, and elevated total cholesterol. Chi-square analyses and independent samples *t*-tests showed no significant associations among covariates in the analyses, which included cardiac index, atrial fibrillation, diabetes, and elevated cholesterol

($p > 0.05$ for all). See Table 1 for between group differences for participants with and without a history of hypertension on medical and demographic characteristics.

Hypertension and Cerebral Perfusion

Table 2 presents the effects of hypertension history on total and lobar perfusion. ANCOVA analyses adjusting for cardiac index, and diagnostic history of diabetes, atrial fibrillation, and elevated total cholesterol showed that the effects of hypertension on total brain perfusion approached significance ($F(1,52) = 3.60, p = 0.06$). A diagnostic history of hypertension was associated with lower total brain perfusion. Significant effects emerged for lower temporal ($F(1,52) = 4.53, p = 0.04$) and occipital lobe perfusion ($F(1,52) = 5.08, p = 0.03$). There was no such pattern for frontal and parietal lobe perfusion ($p > 0.05$). Bivariate correlations showed no association between age and total brain perfusion in this sample and thus analyses were not conducted again with age as a covariate.

Hypertension and Cortical Thickness

Refer to Table 3 for a comparison of cortical thickness between participants with and without a history of hypertension. After accounting for medical variables, history of hypertension demonstrated a significant main effect on total brain cortical thickness ($F(1,52) = 4.57, p = 0.04$). Participants with hypertension had reduced cortical thickness relative to those without such history. To clarify these effects, additional ANCOVA analyses revealed that compared to those without a hypertensive history, a history of hypertension was associated with decreased thickness of the frontal ($F(1,52) = 7.02, p = 0.01$), temporal ($F(1,52) = 4.43, p = 0.04$), and parietal ($F(1,52) = 3.88, p = 0.05$) lobe cortices. This pattern did not emerge for the occipital cortex ($p > 0.05$).

Bivariate correlations revealed a significant association between older age and decreased cortical thickness ($r(56) = -0.53, p < 0.001$). To determine age as a possible confound, ANCOVA analyses controlling for medical variables with the addition of age were repeated. After adjustment for age, hypertension no longer demonstrated a main effect with total brain thickness ($F(1, 51) = 1.44, p = 0.24$); however, there was a trend between hypertension and frontal lobe thickness ($F(1, 51) = 3.19, p = 0.08$).

Cerebral Perfusion and Cortical Thickness

Partial correlations controlling for cardiac index, and diagnostic history of diabetes, atrial fibrillation, and elevated total cholesterol showed that lower total brain perfusion was associated with decreased total brain cortical thickness ($r(52) = 0.39, p = 0.004$). Specifically, reduced brain perfusion correlated with decreased cortical thickness of the frontal ($r(52) = 0.39, p = 0.004$), temporal ($r(52) = 0.35, p = 0.01$), and parietal lobes ($r(52) = 0.39, p = 0.003$). There was a trend for occipital lobe thickness ($r(52) = 0.25, p = 0.07$). These findings remained significant even after adjustment for age ($p < 0.05$ for all).

Antihypertensive Medication, Cerebral Perfusion, and Cortical Thickness

All participants, with the exception of 1, not prescribed antihypertensive medication did not have a history of hypertension. Analyses examined differences on total brain perfusion and thickness between participants prescribed and not prescribed antihypertensive drugs.

Antihypertensive medication did not demonstrate a significant association with total cerebral perfusion ($p = 0.07$) or total cortical thickness ($p = 0.10$). Although findings were not significant and thus limit interpretability, those prescribed hypertensive medications exhibited lower total brain perfusion and decreased brain thickness than those participants not prescribed antihypertensives. Of note, the above findings remained non-significant after accounting for age ($p > 0.05$ for all).

Discussion

This is the first study to examine the interrelationships among hypertension, cerebral blood flow, and cortical thickness. Hypertension was common in this representative sample of older adults with varying levels of vascular disease. This study provides preliminary findings that hypertension is associated with cerebral hypoperfusion and that reduced cortical thickness.^{11,12} We further extend the current literature by showing that antihypertensive drugs may not be associated with cortical perfusion or thickness and suggests that this relationship is more complicated than typically believed. Many aspects of these findings warrant further discussion.

We found that a diagnostic history of hypertension was associated with lower total and regional cerebral perfusion. Hypertension is associated with cerebrovascular disease, including a well-documented right-sided shift in the cerebral autoregulatory curve resulting in overall higher perfusion pressure.³⁹⁻⁴¹ Hypertension is also linked with micro- and macrovascular injury (e.g., vascular narrowing, atherosclerosis, endothelial dysfunction) that contribute to decreases in cerebral blood flow.^{39,42-45} As a result, decreased oxygenation to key brain regions (e.g., hippocampus) may increase risk for dementia (e.g., Alzheimer's disease) in hypertensive older adults.² Indeed, hypertension was associated with lower temporal lobe perfusion in the current study, a region of the brain comprised of structures (e.g., hippocampus) sensitive to hypoxia and implicated in the pathogenesis of Alzheimer's disease.⁴⁶⁻⁴⁸ Prospective studies are needed to elucidate the associations among hypertension, cerebral blood flow, and the development of dementia neuropathology.

Relative to those without hypertension, participants with a hypertensive history exhibited reduced total and lobar cortical thickness. Past work also shows that hypertension is associated with atrophy of the frontal, temporal, and posterior brain regions.⁴⁹⁻⁵¹ Although the evidence is limited, recent work now also extends the impact of hypertension to decreased cortical thickness.^{10,11} This is concerning, as reduced thickness of the cortex may triple the risk for cognitive decline and is an important predictor of Alzheimer's disease conversion.^{7,9} Based on this study and others, a possible explanation for decreased cortical thickness in hypertensive individuals may involve reduced brain perfusion. Hypertension is linked with ischemic injury (e.g., white matter hyperintensities) that often leads to brain shrinkage.⁵²⁻⁵⁵ Cerebral hypoperfusion accelerates brain atrophy in medical and neurological populations^{8,56,57} and recent work demonstrates its association with cortical thickness in older adults.³⁰ Nevertheless, the effects of hypertension on cortical thickness was attenuated after age was entered as covariate. This is perhaps not surprising given the close association between older age and brain shrinkage. Thus, it is possible that hypertension may exacerbate age-related brain structure changes rather than fully account

for it and prospective studies are needed to test this possibility. Longitudinal studies with larger samples are also needed to determine whether hypertension increases risk for dementia via cerebral hypoperfusion and its subsequent effects on the brain structure.

The current study found no association between antihypertensive treatment and total brain perfusion or thickness. Such findings raise the possibility that antihypertensive treatment may have attenuated, but not improved, the development of brain pathology associated with hypertension in this sample. Past work shows blood pressure lowering improves cerebral blood flow and promotes positive neurocognitive outcomes, including decreased risk for dementia.^{20,58-61} However, the literature is not consistent as past studies also show limited effects for antihypertensive therapy on the cerebral structure²³ and it is possible that brain damage from long-term periods of uncontrolled hypertension may not be reversible, even with improvements in cerebral blood flow.

Unfortunately, the current study offers limited insight into the effects of antihypertensive medication on the brain because of several study limitations, including lack of a pre- and post-study design, and we did not account for treatment intensity or duration. Recent work in older adults demonstrates that intensive treatment with blood pressure medication to a target of <130/80 mm Hg increased cerebral blood flow, but no such pattern emerged in a comparison group that received treatment to a target of >140/85 mm Hg.⁶⁰ Tryambake and colleagues (2013) theorized that intensive treatment may be most effective to attenuate adverse brain changes. However, it has also been proposed that hypotension subsequent to antihypertensive treatment increases risk for cardiovascular disease and accelerates brain atrophy and white matter disease.^{62,63} Indeed, blood pressure lowering may actually have detrimental brain effects possibly due to heightened sensitivity to ischemia during brief drops in arterial pressure.^{39,63-66} As an example, recent work suggests hypertension interacts with long-term blood pressure fluctuations to exacerbate white matter disease among elderly individuals.⁶⁶ Prospective studies that use control and comparison groups are needed to elucidate the acute and long-term impact of blood pressure lowering on neurocognitive outcomes and identify underlying mechanisms.

Our findings are limited in several ways. First, the relatively modest sample size of the current study limits the external validity of our findings and larger studies are needed to confirm the effects of hypertension on the brain. Interestingly, the current study found an effect for hypertension on occipital lobe perfusion, but not on occipital cortical thickness. The exact reason for this finding is not entirely clear, but further suggests the association between hypertension, cerebral perfusion, and brain structure is complex. Larger studies that utilize control and comparison groups would also help elucidate the exact nature and pattern of regional brain injury associated with hypertension. These studies should also examine the interactive effects between hypertension and other factors that contribute to poor brain outcomes in older adults such as demographic factors (e.g., age), and CVD risk factors (e.g., diabetes).

We also examined diagnostic history of hypertension, which is indeed believed to be a sensitive marker of the lifelong cumulative effects of uncontrolled hypertension on the brain.^{67,68} Supporting this notion is past work that shows longer duration of hypertension

predicts greater reductions in cerebral blood flow.⁶⁹ Although resting blood pressure would allow for a more direct examination of hypertension status, this measurement has been shown to lack sensitivity to brain outcomes in cardiovascular disease patients⁶⁸ and is possibly confounded by the prevalent use of antihypertensive medications in older adult populations. In turn, prospective studies that use 24-hour ambulatory monitoring would be most effective in elucidating the interrelationships among hypertension, brain perfusion, and cerebral morphometry. Such studies would also help clarify the role of blood pressure fluctuations (via blood pressure lowering or otherwise) on the brain. Finally, randomized controlled trials that account for blood pressure treatment intensity and duration and implement pre- and post-study designs are also needed to better understand the impact and directionality between antihypertensive therapy and neurocognitive outcomes.

Conclusions

In brief summary, the current study suggests that a diagnostic history of hypertension is associated with decreased cerebral perfusion and reduced cortical thickness. Antihypertensive use was not associated with improved cerebral blood flow or cortical thickness. Prospective studies are needed to elucidate the effects of hypertension on the brain and subsequent risk for neurological conditions such as Alzheimer's disease.

Acknowledgments

Support for this work included National Institutes of Health Grant R01HL084178.

References

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. *Circulation*. 2013; 127:e6–e245. [PubMed: 23239837]
2. Kivipelto M, Helkala E, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ*. 2001; 322:1447–1451. [PubMed: 11408299]
3. Posner HB, Tang MX, Luchsinger J. The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function. *Neurology*. 2000; 58:1175–1181. [PubMed: 11971083]
4. DeCarli C, Miller BL, Swan GE, Reed T, Wolf PA, Garner J, Jack L, Carmelli D. Predictors of brain morphology for the men of the NHLBI twin study. *Stroke; a journal of cerebral circulation*. 1999; 30:529–536.
5. Beauchet O, Celle S, Roche F, et al. Blood pressure levels and brain volume reduction: a systematic review and meta-analysis. *J Hypertens*. 2013; 31:1502–1516. [PubMed: 23811995]
6. Swan GE, DeCarli C, Miller BL, et al. Association of midlife blood pressure to late-life cognitive decline and brain morphology. *Neurology*. 1998; 51:986–993. [PubMed: 9781518]
7. Querbes O, Aubry F, Pariente J, et al. Early diagnosis of Alzheimer's disease using cortical thickness: impact of cognitive reserve. *Brain*. 2009; 132:2036–2047. [PubMed: 19439419]
8. Austin BP, Nair VA, Meier TB, et al. Effects of hypoperfusion in Alzheimer's disease. *J Alzheimers Dis*. 2011; 26:123–133. [PubMed: 21971457]
9. Dickerson BC, Wolk DA, et al. MRI cortical thickness biomarker predicts AD-like CSF and cognitive decline in normal adults. *Neurology*. 2012; 78:84–90. [PubMed: 22189451]
10. Leritz EC, Salat DH, et al. Thickness of the human cerebral cortex is associated with metrics of cerebrovascular health in a normative sample of community dwelling older adults. *Neuroimage*. 2011; 54:2659–2671. [PubMed: 21035552]

11. Seo SW, Lee JM, Im K, et al. Cardiovascular risk factors cause cortical thinning in cognitive impaired patients: relationships among cardiovascular risk factors, white matter hyperintensities, and cortical atrophy. *Alzheimer Dis Assoc Disord*. 2012; 26:106–112. [PubMed: 21946011]
12. Waldstein SR, Lefkowitz DM, Siegel EL, et al. Reduced cerebral blood flow in older men with higher levels of blood pressure. *J Hypertens*. 2010; 28:993–998. [PubMed: 20408259]
13. Fujishima M, Ibayashi S, Fuji K, et al. Cerebral blood flow and brain function in hypertension. *Hypertension Res*. 1995; 18:111–117.
14. Alosco ML, Gunstad J, Jerskey BA, et al. The adverse effects of reduced cerebral perfusion on cognition and brain structure in older adults with cardiovascular disease. *Brain Behav*. 2013; 3:626–636. [PubMed: 24363966]
15. Reiman EM, Caselli RJ, Yun LS, Chen K, Bandy D, Minoshima S, Thibodeau SN, Osborne D. Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein E. *N Engl J Med*. 1996; 334:752–758. [PubMed: 8592548]
16. Reiman EM, Chen K, Alexander GE, Caselli RJ, Bandy D, Osborne D, Saunders AM, Hardy J. Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia. *Proc Natl Acad Sci U S A*. 2004; 101:284–289. [PubMed: 14688411]
17. Espeseth T, Westlye LT, Fjell AM, Walhovd KB, Rootwelt H, Reinvang I. Accelerated age-related cortical thinning in healthy carriers of apolipoprotein E epsilon 4. *Neurobiol Aging*. 2008; 29:329–340. [PubMed: 17161508]
18. Forette F, Seux ML, Staessen JA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *Arch Intern Med*. 2002; 162:2046–2052. [PubMed: 12374512]
19. Chalmers J, Arima H. Management of hypertension: evidence from the Blood Pressure Lowering Treatment Trialists' Collaboration and from major clinical trials. *Pol Arch Med Wewn*. 2009; 119:373–380. [PubMed: 19694219]
20. Nagata R, Kawabe K, Ikeda K. Olmesartan, an angiotensin II receptor blocker, restores cerebral hypoperfusion in elderly patients with hypertension. *J Stroke Cerebrovasc Dis*. 2010; 19:236–240. [PubMed: 20434053]
21. Firbank MJ, Wiseman RM, Burton EJ, et al. Brain atrophy and whiter hyperintensity change in older adults and relationship to blood pressure. Brain atrophy, WMH, change an dblood pressure. *J Neurol*. 2007; 254:713–721. [PubMed: 17446997]
22. Peters R, Beckett N, Forette F, Tuomilehto J, Clarke R, Ritchie C, Waldman A, Walton I, Poulter R, Ma S, Comsa M, Burch L, Fletcher A, Bulpitt C. HYVET Investigators. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. *Lancet Neurol*. 2008; 7:683–689. [PubMed: 18614402]
23. Jennings JR, Mendelson DN, Muldoon MF, et al. Regional grey matter shrinks in hypertensive individuals despite successful lowering of blood pressure. *J Hum Hypertens*. 2012; 26:295–305. [PubMed: 21490622]
24. Sare GM, Gray LJ, Bath PM. Effect of antihypertensive agents on cerebral blood flow and flow velocity in acute ischaemic stroke: systematic review of controlled studies. *J Hypertens*. 2008; 26:1058–1064. [PubMed: 18475140]
25. Luh WM, Wong EC, Bandettini PA, Hyde JS. QUIPSS II with thin-slice TI₁ periodic saturation: a method for improving accuracy of quantitative perfusion imaging using pulsed arterial spin labeling. *Magn Reson Med*. 1999; 41:1246–1254. [PubMed: 10371458]
26. Dale AM, Fischl B, Sereno MI. Cortical Surface-Based Analysis I: Segmentation and Surface Reconstruction. *NeuroImage*. 1999; 9:179–194. 1999. [PubMed: 9931268]
27. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis II: Inflation, flattening, and a surface-based coordinate system. *Neuroimage*. 1999; 9:195–207. [PubMed: 9931269]
28. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A*. 2000; 97:11050–11055. [PubMed: 10984517]

29. Fischl B, Salat DH, Busa E, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*. 2002; 33:341–355. [PubMed: 11832223]
30. Fischl B, van der Kouwe A, Destrieux C, et al. Automatically parcellating the human cerebral cortex. *Cereb Cortex*. 2004; 14:11–22. [PubMed: 14654453]
31. Wright PJ, Mouglin OE, Totman JJ, et al. Water proton T₁ measurements in brain tissue at 7, 3, and 1.5T using IR-EPI, IR-TSE, and MPRAGE: results and optimization. *MAGMA*. 2008; 21:121–130. [PubMed: 18259791]
32. Zhu DC, Penn RD. Full-brain T₁ mapping through inversion recovery fast spin echo imaging with time-efficient slice ordering. *Magn Reson Med*. 2005; 54:725–731. [PubMed: 16086307]
33. Stanisz GJ, Odobina EE, Pun J, et al. T₁, T₂ Relaxation and magnetization transfer in tissue at 3T. *Magn Reson Med*. 2005; 54:507–512. [PubMed: 16086319]
34. Ashburner J. Computational anatomy with the SPM software. *Magn Reson Imag*. 2009; 27:1163–1174.
35. Ashburner J, Friston KJ. Computing average shaped tissue probability templates. *Neuroimage*. 2008; 45:333–341. [PubMed: 19146961]
36. Cox RW. AFNI: Software for Analysis and Visualization of Functional Magnetic Resonance Neuroimages. *Compu Biomed Res*. 1996; 29:162–173.
37. Lang RM, Bierig M, Devereux RB, et al. Chamber Quantification Writing Group. American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. *J Am Soc Echocardiogr*. 2005; 18:1440–1463. [PubMed: 16376782]
38. Desikan RS, Segonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*. 2006; 31:968–980. [PubMed: 16530430]
39. Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev*. 1990; 2:161–192. [PubMed: 2201348]
40. Ruland S, Aiyagari V. Cerebral autoregulation and blood pressure lowering. *Hypertension*. 2007; 49:977–978. [PubMed: 17353508]
41. Carnevale D, Lembo G. Hypertension and cerebrovascular dysfunction Acute and chronic brain pathological alterations. *High Blood Press Cardiovas Prev*. 2010; 17:191–233.
42. Novak V, Chowdhary A, Farrar B, et al. Altered cerebral vasoregulation in hypertension and stroke. *Neurology*. 2003; 60:1657–1663. [PubMed: 12771258]
43. Bomboi G, Castello L, Cosentino F, et al. Alzheimer's disease and endothelial dysfunction. *Neurol Sci*. 2010; 31:1–8. [PubMed: 19838624]
44. Tang JP, Xu ZQ, Douglas FL, Rakhit A, Melethil S. Increased blood-brain barrier permeability of amino acids in chronic hypertension. *Life Sci*. 1993; 53:PL417–PL420. [PubMed: 7902950]
45. Cohen RA. Hypertension and cerebral blood flow: implications for the development of vascular cognitive impairment in the elderly. *Stroke*. 2007; 38:1715–1717. [PubMed: 17510446]
46. Freund TF, Buzsaki G, Prohaska OJ, et al. Simultaneous recording of local electrical activity, partial oxygen tension and temperature in the rat hippocampus with a chamber-type microelectrode. Effects of anesthesia, ischemia and epilepsy. *Neuroscience*. 1989; 28:539–549. [PubMed: 2710329]
47. Zola-Morgan S, Squire LR, Amaral DG. Human amnesia and the medial temporal region: eduring memory impairment following bilateral lesion limited to the field CA1 of the hippocampus. *J Neurosci*. 1986; 6:2950–2967. [PubMed: 3760943]
48. Hyman BT, Damasio AR, Van Hoesen GW, et al. Alzheimer's disease cell-specific pathology isolates the hippocampal formation. *Science*. 1984; 225:1168–1170. [PubMed: 6474172]
49. Raz N, Rodrigue KM, Acker JD. hypertension and the brain: vulnerability of the prefrontal regions and executive functions. *Behavioral Neuroscience*. 2003; 117
50. Raz N, Rodrigue KM, Haacke EM. Brain aging and its modifiers: insights from in vivo neuromorphometry and susceptibility weighted imaging. *Ann N Y Acad Sci*. 2007; 1097:84–93. [PubMed: 17413014]

51. Raz N, Rodrigue KM, Kennedy KM, Acker JD. Vascular health and longitudinal changes in brain and cognition in middle-aged and older adults. *Neuropsychology*. 2007; 21:149–157. [PubMed: 17402815]
52. Havlik RJ, Foley DJ, Sayer B, Masaki K, White L, Launer LJ. Variability in Midlife Systolic Blood Pressure is Related to Late-Life Brain White Matter Lesions. *Stroke*. 2002; 33:26–30. [PubMed: 11779884]
53. Schmahmann JD, Smith EE, Eichler FS, Filley CM. Cerebral white matter: neuroanatomy, clinical neurology, and neurobehavioral correlates. *Ann N Y Acad Sci*. 2008; 1142:266–309. [PubMed: 18990132]
54. Knopman DS. Dementia and cerebrovascular disease. *Mayo Clinic Proceedings*. 2006; 81:223–230. [PubMed: 16471078]
55. Raz N, Rodrigue KM. Differential aging of the brain: patterns, cognitive correlates and modifiers. *Neurosci Biobehav Rev*. 2006; 30:730–748. [PubMed: 16919333]
56. Van Elderen SG, Brandts A, van der Grond J, et al. Cerebral perfusion and aortic stiffness are independent predictors of white matter brain atrophy in type 1 diabetic patients assessed with magnetic resonance imaging. *Diabetes Care*. 2011; 34:459–463. [PubMed: 21216862]
57. Aoi MC, Hu K, Lo MT, Selim M, Olufsen MS, Novak V. Impaired cerebral autoregulation is associated with brain atrophy and worse functional status in chronic ischemic stroke. *PLoS One*. 2012; 7:e46794. [PubMed: 23071639]
58. Lipsitz LA, Gagnon M, Vyas M, et al. Antihypertensive therapy increases cerebral blood flow and carotid distensibility in hypertensive elderly subjects. *Hypertension*. 2005; 45:216–221. [PubMed: 15655124]
59. Lipsitz LA, Mukai S, Hamner J, Gagnon M, Babikian V. Dynamic regulation of middle cerebral artery blood flow velocity in aging and hypertension. *Stroke*. 2000; 31:1897–1903. [PubMed: 10926954]
60. Tryambake D, He J, Firkbank MJ, et al. Intensive blood pressure lowering increases cerebral blood flow in older subjects with hypertension. *Hypertension*. 2013; 61:1309–1315. [PubMed: 23529166]
61. Shah K, Qureshi SU, Johnson M, et al. Does use of antihypertensive drugs affect the incidence or progression of dementia? A systematic review. *Am J Geriatr Pharmacother*. 2009; 7:250–261. [PubMed: 19948301]
62. Fagan SC, Payne LW, Houtekier SC. Risk of cerebral hypoperfusion with antihypertensive therapy. *DICP*. 1989; 23:957–962. [PubMed: 2690472]
63. Graham DI. Ischaemic brain damage of cerebral perfusion failure type after treatment of severe hypertension. *Br Med J*. 1975; 4:739. [PubMed: 1212586]
64. Cruikshank JM, Thorp JM, Zacharis FJ. Benefits and potential harm of lowering hypertension. *Lancet*. 1987; 1:581–584. [PubMed: 2881129]
65. Immink RV, van den Born BH, van Montfrans GA, Koopmans RP, Karemaker JM, van Lieshout JJ. Impaired cerebral autoregulation in patients with malignant hypertension. *Circulation*. 2004; 110:2241–2245. [PubMed: 15466625]
66. Brickman AM, Reitz C, Luchsinger JA, et al. Long-term blood pressure fluctuation and cerebrovascular disease in an elderly cohort. *Arch Neurol*. 2010; 67:564–569. [PubMed: 20457955]
67. Waldstein SR, Brown JR, Maier KJ, et al. Diagnosis of hypertension and high blood pressure levels negatively affect cognitive function in older adults. *Ann Behav Med*. 2005; 29:174–180. [PubMed: 15946111]
68. Alosco ML, Brickman AM, Spitznagel MB, et al. The independent association of hypertension with cognitive function among older adults with heart failure. *J Neurol Sci*. 2012; 323:216–220. [PubMed: 23026535]
69. Beason-Held LL, Moghekar A, Zonderman AB, Kraut MA, Resnick SM. Longitudinal changes in cerebral blood flow in the older hypertensive brain. *Stroke*. 2007; 38:1766. [PubMed: 17510458]

Table 1
Demographic and Medical Characteristics of Older Adults with and without Hypertension

Demographic Characteristics	Hypertension	No Hypertension	Total Sample	t/χ^2
<i>N</i>	23	35	58	
Age, mean (SD)	69.61 (9.13)	64.29 (9.21)	66.40 (9.47)	2.16*
Gender (% Women)	47.8	65.7	58.6	1.83
Years of Education, mean (SD)	15.91 (2.63)	16.15 (2.55)	16.05 (2.56)	-.34
Race (% Caucasian)	91.3	97.2	94.8	4.37
Medical Characteristics				
Cardiac Index, mean (SD)	2.80 (.61)	2.75 (.54)	2.77 (.56)	.31
Coronary Artery Disease (%)	30.4	11.4	19.0	3.26
Atrial Fibrillation (%)	8.7	8.6	8.6	.00
Diabetes (%)	17.4	2.9	8.6	3.72
Elevated Total Cholesterol (%)	73.9	34.3	50.0	8.72**
Antihyperlipidemics (%)	82.6	34.3	53.4	13.03**
Antihypertensive Agents (%)	95.7	22.9	51.7	29.45**

Note.

*
 $p < 0.05$;

**
 $p < 0.01$;

test statistics compare between group differences for those with and without hypertension

Table 2

The Effects of Hypertension on Cerebral Perfusion

	Total Brain	Frontal Lobe	Temporal Lobe	Parietal Lobe	Occipital Lobe
Hypertension (N = 23)	47.33 (7.14)	45.65 (7.62)	45.42 (8.03)	48.27 (7.27)	49.99 (10.50)
No Hypertension (N = 35)	49.96 (6.57)	46.80 (6.57)	48.00 (6.57)	50.83 (7.34)	54.21 (10.01)
<i>F</i>	3.60 (p = .06)	0.43	4.53*	1.66	5.08*
Partial-Eta	.07	.01	.08	.03	.09

Note.

* $p < 0.05$;

Values reflect means and standard deviations; units are ml/mg/s

Analyses adjusted for cardiac index, and diagnostic history of diabetes, atrial fibrillation, and elevated total cholesterol

Table 3**The Effects of Hypertension on Cortical Thickness**

	Total Brain	Frontal Lobe	Temporal Lobe	Parietal Lobe	Occipital Lobe
Hypertension (N = 23)	2.42 (.13)	2.53 (.12)	2.72 (.12)	2.35 (.14)	2.06 (.15)
No Hypertension (N = 35)	2.46 (.13)	2.59 (.13)	2.78 (.16)	2.40 (.15)	2.08 (.12)
F	4.57*	7.02*	4.43*	3.88 (p = 0.05)	0.90
Partial Eta	.08	.12	.08	.07	.02

Note.

* $p < 0.05$;

Values reflect means and standard deviations; units are mm

Analyses adjusted for cardiac index, and diagnostic history of diabetes, atrial fibrillation, and elevated total cholesterol