Hypertension and Cerebral Vasoreactivity. A Continuous Arterial Spin Labeling Magnetic Resonance Imaging Study

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Hypertension published online Sep 27, 2010;
DOI: 10.1161/HYPERTENSIONAHA.110.160002
Hypertension is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0194-911X. Online ISSN: 1524-4563

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Abstract—Hypertension is associated with microvascular and macrovascular brain injury but its direct influence on the cerebral circulation is not fully clear. Our objective was to investigate the association of hypertension with global and regional cerebral vasoreactivity to CO_2 using continuous arterial spin labeling MRI, independent of stroke and white matter hyperintensities. Participants (n=62; mean age: 66.7±1.0 years, 55% women, 84% white, 65% hypertension, 47% stroke) underwent arterial spin labeling perfusion MRI during normal breathing, 5% CO_2 rebreathing, and hyperventilation, as well as 24-hour ambulatory blood pressure monitoring. Vasoreactivity was the slope of the regression between cerebral perfusion and end-tidal CO_2. White matter hyperintensity volumes were quantified. Nighttime dipping was calculated as the percentage decline in nighttime/daytime blood pressure. After accounting for stroke and white matter hyperintensity volume, hypertensive participants had lower global vasoreactivity (1.11±0.13 versus 0.43±0.1 mL/100 g per minute per millimeter of mercury; P=0.0012). Regionally, this was significant in the frontal, temporal, and parietal lobes. Higher mean systolic blood pressure was associated with lower vasoreactivity (decreased by 0.11 U/10-mm Hg increase in systolic blood pressure; P=0.04), but nighttime dipping was not (P=0.2). The magnitude of decrease in vasoreactivity in hypertension without stroke was comparable to the magnitude of decrease in vasoreactivity in stroke without hypertension. Hypertension has a direct negative effect on the cerebrovascular circulation independent of white matter hyperintensities and stroke that is comparable to that seen with stroke. Because lower vasoreactivity is associated with poor outcomes, studies of the impact of antihypertensive on vasoreactivity are important. **(*Hypertension*. 2010;56:00-00.)**

Key Words: hypertension ■ cerebrovascular circulation ■ vasoconstriction ■ vasodilation

Decline in cerebrovascular reactivity is associated with cognitive decline,[1–4] slower gait speed, and possibly falls.[5] Previous studies suggest that hypertension may have an influence on cerebrovascular reactivity.[6] Most of these studies have assessed cerebrovascular reactivity in hypertension by measuring changes in cerebral blood flow at the middle cerebral artery in response to changes to end-tidal carbon dioxide (CO_2) using transcranial Doppler (TCD).[7] Although these studies have shown that hypertensives may have lower cerebral vasoreactivity to CO_2, gaps in our knowledge remain unanswered. Hypertension is a major risk factor for stroke and white matter hyperintensities (WMHs), both associated with impaired cerebral vasoreactivity.[8,9] TCD cannot assess whether the lower vasoreactivity noted in hypertension is related or independent of stroke or WMH. TCD, moreover, does not provide simultaneous assessment of vasoreactivity in multiple brain regions. Identifying specific regions that may have lower vasoreactivity in the brain offers an insight to the potential processes by which the brain is affected by hypertension.

Continuous arterial spin labeling (CASL) perfusion MRI can detect cerebral perfusion changes, provide detailed cerebral blood flow mapping in several brain regions, and simultaneously assesses structural brain changes.[10–12] CASL-MRI, hence, addresses the gaps in our knowledge regarding hypertension and cerebral vasoreactivity. Our group has validated the use of CASL-MRI to assess cerebral vasoreactivity in diabetics and stroke survivors.[8,13] In this study, we expanded the application of CASL-MRI to assess the relation between hypertension and cerebral vasoreactivity.

Hypertension is also associated with changes in circadian rhythms, most notably lack of nighttime dipping.[14] This, in turn, has been associated with stroke and greater brain atrophy.[15,16] It is not known whether the potentially impaired cerebrovascular reactivity seen in hypertension is related to elevated blood pressure, lower nighttime dipping, or both.

Our objective was to determine the association between hypertension and cerebral vasoreactivity to CO_2, after accounting for WMH and previous stroke using CASL-MRI. Our second objective was to investigate the relation between nighttime dipping and vasoreactivity.

Methods

Subjects

Potential subjects were invited to the study using local advertisement in the greater Boston area. All of the evaluations were conducted at

Received July 22, 2010; first decision August 9, 2010; revision accepted August 17, 2010.

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Hypertension **is available at http://hyper.ahajournals.org** **DOI: 10.1161/HYPERTENSIONAHA.110.160002**

the Beth Israel Deaconess Medical Center. Inclusion criteria were age ≥50 years and able to perform study procedures, including ambulatory blood pressure monitoring (ABPM) and brain MRI. Individuals with stroke were allowed in this study as long as they were >6 months after acute event that affected less than one third of middle cerebral artery territory and had a modified Rankin Scale score <4. The average time post stroke was 6.1 years. Individuals who were receiving antihypertensive medications were also allowed, but these medications were gradually tapered over 3 days and discontinued before the study for ≥2 days. Anticoagulation and antihyperlipidemic medications were allowed.

Exclusion criteria were diabetes mellitus (history or hemoglobin A1C levels >7.0 mg/dL), dementia or Alzheimer disease, coronary heart disease or congestive heart failure (identified by history, medications, or clinical examination), hospitalization, chronic renal and liver disease, transplantation, active cancer treatment or previous exposure to chemotherapy or radiation, or symptomatic arrhythmias. The study protocol and the investigators adhered to the principles of the Declaration of Helsinki and Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001. All of the subjects provided written informed consent, and the protocol was approved by the Beth Israel Deaconess Medical Center Institutional Review Board.

We screened potential subjects with detailed medical history and physical and neurological examinations, ECG, and routine laboratory tests. A trained research nurse performed manual blood pressure measurements according to the American Heart Association guidelines.[17] If the participant was receiving antihypertensive medications, then he or she was given instructions to taper off the medication according to a standard protocol. Participants were then admitted for 2 days to the General Clinical Research Center. Two manual blood pressure and heart rate measurements were performed 3 times per day for 2 days. Cognitive assessment was performed using the mini-mental status examination.[18]

Ambulatory Blood Pressure Monitoring

ABPM was recorded from 8:00 AM the first admission day to 8:00 AM the next day using a portable automatic monitor Dynapulse (Pulse Metric, Inc). This monitor has been previously validated against intra-arterial blood pressure measurement with a correlation of 98% ($P<0.001$).[19] Systolic blood pressure (SBP) and diastolic blood pressure (DBP) and heart rate were measured at 20-minute intervals during the day and at 30-minute intervals during the night. They were asked to follow their daily routine resembling the usual daily activities at home documented in a personal diary completed before study initiation. All of the activities performed during the daytime and the sleep and wake times were confirmed using the diary and direct observation.

Dipping and Hypertension Definition

Participants were considered hypertensive if they had history of hypertension or were receiving antihypertensives. Those who were not hypertensive based on their history or medication profile but had elevated blood pressure measurements (≥135/85 mm Hg on ABPM[20,21] and average casual blood pressure ≥140/90 mm Hg) were also considered hypertensive (only 2 participants). Dipping was calculated according to the standard formula: (daytime blood pressure − nighttime blood pressure)/daytime blood pressure × 100. Those who had >10% nighttime decline in SBP or DBP were considered dippers.[20,22]

MRI Protocol and Data Analysis

Brain imaging protocol is described elsewhere[8,23] and was performed 3 hours after completing the ABPM monitoring at the 3T MRI scanner. Briefly, high-resolution anatomic image 3D magnetization prepared rapid gradient echoes were acquired to quantify volume of white matter and gray matter (in cubic centimeters). WMH volume was measured on fluid-attenuated inversion recovery images. In our analyses, we used the WMH volume (in cubic centimeters) divided by intracranial volume to account for head size differences between participants. Cerebral perfusion was measured using CASL. CASL technology uses proton labeling of the water molecules in the blood flowing in the blood vessels to allow for accurate and reproducible measures of perfusion.[11] Labeled and unlabeled images were collected over 2-minute periods during normal breathing, CO_2 rebreathing with 95% air and 5% CO_2 (hypercapnia), and hyperventilation (hypocapnia). Two scans were obtained during each phase, and data were then averaged. End-tidal CO_2 was continuously monitored and averaged over 15-second intervals. Cerebral vasoreactivity was calculated as the slope of the regression between cerebral perfusion and end-tidal CO_2, in units of milliliters per 100 grams per minute per millimeter of mercury, during normal breathing, CO_2 rebreathing, and hyperventilation. We calculated a global cerebral vasoreactivity slope and regional vasoreactivity slopes in the frontal, parietal, temporal, occipital, and cerebellar regions. In the stroke participants, vasoreactivity measures were calculated for both the stroke and nonstroke hemispheres (please see the online Data Supplement at http://hyper.ahajournals.org for more details).

Statistical Analyses

We used t test or χ^2 to compare characteristics of the hypertensive and normotensive groups. We used general linear models to investigate the association between hypertension and cerebral vasoreactivity (global and regional). Models were adjusted for age, sex, race/ethnicity, body mass index, antihypertensives, and WMH volume/intracranial cavity. We included WMH because of its effect on vasoreactivity and its close association with hypertension.[9] We calculated the least-square mean vasoreactivity adjusted for covariates when comparing the hypertensive and normotensive groups. Effect size for hypertension was measured using partial eta square (η^2).[24] Higher values indicate stronger effect size.

We used regression analysis to investigate the association between blood pressure and dipping magnitude (both as a continuous measures) with cerebral vasoreactivity. Models were adjusted for the same covariates. We reported the regression coefficient per 10 mm Hg in the blood pressure analyses and per 10% in the dipping analyses, adjusted for these covariates. Effect size was measured by partial correlations.

Finally, we performed stratified analysis by stroke. We used generalized linear models adjusted for the same covariates, except for stroke. We performed 2 sets of analyses in the stroke group (stroke side and opposite side). To assess if there was regional variation in the impact of hypertension on cerebral vasoreactivity, we used mixed models for correlated data for these analyses, because there was a high correlation between the brain regions within an individual.[25] We calculated difference in the adjusted least-square mean vasoreactivity between hypertensives and normotensives by region. We then tested whether the differences by region were significant.

Results

Sample

Of the 68 participants, 6 did not have complete ABPM data. Therefore, data on 62 individuals were used for this analysis (mean age: 66.7±1.0 years; 55% women; 84% white). Of those, 40 (65%) were hypertensive (38 were on antihypertensives or were diagnosed with hypertension; and an additional 2 had elevated blood pressure based on ABPM and casual blood pressure measurements). As shown in Table 1, there were no significant differences between hypertensive and normotensive participants in demographic, clinical, laboratory, and brain gray and white matter volume measures. ABPM indices and lipid measures were different between the 2 groups. Global WMH volume was higher in the hypertensive group, but this did not reach statistical significance.

Table 1. Demographic, Vascular, and Brain MRI Characteristics of the Normotensive and Hypertensive Participants

Characteristic	Normotensives	Hypertensives	*P*
N	22	40	
Age, y	67±2	67±1	0.96
Women, %	56	54	0.81
White, %	83	84	0.98
Body mass index, kg/m^2	25.8±0.9	26.1±0.7	0.77
Alcohol drinks per week	1.7±0.8	7.9±2.9	0.18
Current smokers, %	6	11	0.71
Stroke, %	32	57	0.052
Mini-mental state examination	28.1±0.5	26.9±1	0.097
Blood pressure			
SBP, mm Hg	118±1	133±2	<0.0001
DBP, mm Hg	68±1	68±1	0.9
24-h ABPM			
SBP, mm Hg	119±2	136±2	<0.0001
DBP, mm Hg	63±1	67±1	0.049
Daytime SBP, mm Hg	121±2	137±2	<0.0001
Daytime DBP, mm Hg	65±1	68±1	0.11
Nighttime SBP, mm Hg	115±2	133±2	<0.0001
Nighttime DBP, mm Hg	59±2	64±1	0.033
Heart rate, bpm	67±2	67±1	0.89
Dippers, %	54	27	0.03
Laboratory			
Hemoglobin, g/dL	13.8±0.3	13.9±0.2	0.69
Hematocrit, mg/dL	41.1±0.9	40.9±0.5	0.87
Cholesterol, mg/dL	207.4±9.9	184±5	0.02
Low-density lipoprotein, mg/dL	117.5±9.1	94.5±4.1	0.009
Glucose, mg/dL	75.4±3.4	83.4±2.5	0.077
Medications, %			
Hypertension treatment	NA	85	NA
Diuretics		34	NA
Angiotensin-converting enzyme inhibitors		30	NA
β-Blockers		25	NA
Calcium channel blockers		18	NA
Statins	31	50	0.16
Structural brain measures			
Gray matter volume/intracranial volume	0.42±0.008	0.41±0.004	0.41
White matter volume/intracranial volume	0.28±0.008	0.28±0.004	0.62
WMHs, cm^3	8.8±2.8	16.0±3.5	0.12

Numbers are presented as mean±SE for continuous measures or percentages for discrete variables. NA indicates not applicable.

Table 2. Global and Regional Vasoreactivity to CO_2 in Normotensive and Hypertensive Participants

Brain Region	Normotensives	Hypertensives	*P*	Partial η^2
Whole brain	1.11±0.13	0.43±0.1	0.0012	0.32
Cerebellum	0.69±0.13	0.34±0.1	0.0711	0.12
Frontal	1.2±0.15	0.45±0.12	0.002	0.3
Occipital	1.2±0.13	0.52±0.1	0.0013	0.32
Parietal	1.38±0.17	0.47±0.13	0.0007	0.35
Temporal	0.95±0.12	0.37±0.09	0.0015	0.31

Numbers are least-square means adjusted for age, sex, race/ethnicity, body mass index, stroke, antihypertensives, and WMHs/intracranial cavity.

Hypertension and Vasoreactivity

The mean vasoreactivity in the overall sample was 0.78±0.05 mL/100 g per minute per millimeter of mercury. As shown in Table 2, after adjusting for covariates, stroke, and WMH/intracranial cavity volume, hypertensive participants had significantly lower global vasoreactivity compared with normotensives (P=0.0012). The effect size of hypertension was considerably high (partial η^2=0.32). The association of hypertension with lower vasoreactivity was significant in all of the brain regions except the cerebellum. Figure 1 demonstrates the differences in perfusion at baseline and during hypercapnia and hypocapnia phases between a hypertensive and a normotensive participant.

Blood Pressure, Nighttime Dipping, and Vasoreactivity

Higher SBP, but not DBP, was associated with lower vasoreactivity. For each 10-mm Hg increment in SBP, global vasoreactivity decreased by 0.1 Units (partial R^2=0.16) after adjusting for demographics, body mass index, stroke, antihypertensives, and WMH/intracranial volume. Regionally, this was only significant in the parietal and occipital lobes. Dipping status was not associated with vasoreactivity (nondippers: 0.77±0.08 mL/100 g per minute per millimeter of mercury; dippers: 0.77±0.10 mL/100 g per minute per millimeter of mercury; P=0.76). The magnitudes of dipping in SBP and DBP (as continuous measure) were not related to vasoreactivity. These results are shown in the online Data Supplement (please see Table S1, available at http://hyper.ahajournals.org).

Estimating the Magnitude of Decreased Vasoreactivity From Hypertension Without Stroke and From Stroke Without Hypertension

Normotensive participants without stroke had the highest global vasoreactivity. On the other hand, hypertensive participants without stroke had similar vasoreactivity as stroke participants (normotension stroke free: 1.38±0.16 mL/100 g per minute per millimeter of mercury; hypertension stroke free: 0.59±0.010 mL/100 g per minute per millimeter of mercury; P=0.001 after adjusting for covariates; normotension stroke: 0.47±0.40 mL/100 g per minute per millimeter of mercury; hypertension stroke: 0.58±0.35 mL/100 g per minute per millimeter of mercury; P=0.25 in the stroke hemisphere; P=0.57 the nonstroke hemisphere). The regional vasoreactivity results followed the same pattern and are

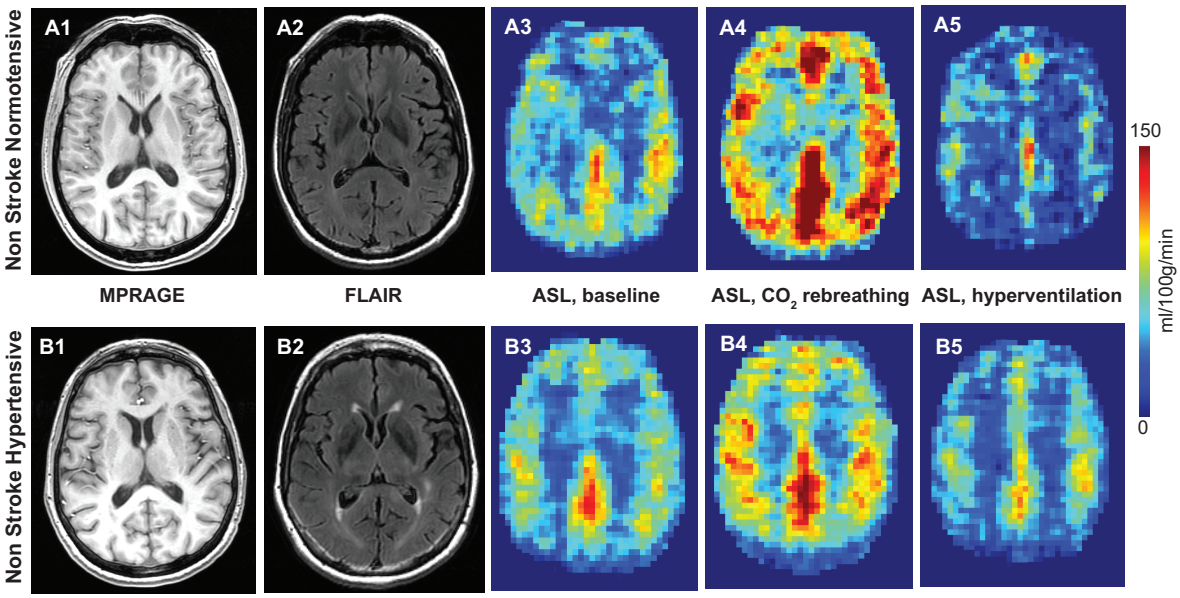

Figure 1. Anatomic and perfusion images for nonstroke normotensive subject (A1 to A5) and nonstroke hypertensive subject (B1 to B5). A1 and B1, Magnetization prepared rapid gradient echo (MPRAGE) images used for brain volume analysis. A2 and B2, Fluid-attenuated inversion recovery (FLAIR) images for WMH analysis. A3 and B3, Baseline cerebral blood flow. A4 and B4, CBF during CO_2 rebreathing. A5 and B5, CBF during hyperventilation. The perfusion scale is 0 to 150 mL/100 g per minute on all CBF maps. Nonstroke normotensive subject has similar baseline CBF, higher CBF during hypercapnia, and lower CBF during hyperventilation as compared with nonstroke hypertensive subject.

shown in Figure 2. Hypertensive participants without stroke had comparable vasoreactivity to those with stroke in all of the regions after adjusting for all of the related covariates. When we compared the hypertension-related differences in vasoreactivity in the various brain regions, the decline was greatest in the parietal and frontal regions in nonstroke hypertensive participants as shown in Table 3.

Discussion

Our findings extend our previous knowledge, which is mostly based on TCD and positron emission tomography scan technology, by demonstrating that hypertension is directly associated with lower cerebral vasoreactivity to CO_2 independent of stroke and WMH. The magnitude of decrease in cerebral vasoreactivity from hypertension in the absence of stroke is comparable to that of stroke. Moreover, there is an inverse association between lower cerebral vasoreactivity and higher SBP but not with nighttime dipping. Regionally, hypertension is associated with lower vasoreactivity in all of the cortical brain regions but is more prominent in the frontal and parietal areas.

To our knowledge, this is the first study using CASL-MRI to assess vasoreactivity in hypertensives. We have reported previously that higher SBP is associated with poor global and regional perfusion using CASL-MRI.[23] Dai et al[26] demonstrated that, in 19 hypertensive participants in the Cardiovascular Health Study, regional blood flow was lower than that in normotensives using CASL-MRI. Hypertension is also associated with lower vasoreactivity, in addition to decreased perfusion. This may further impair the ability to maintain cerebral blood flow during increasing demands and lead to further brain injury. Because lower vasoreactivity maybe associated with cognitive and physical declines,[3,5] this observation may provide a partial explanation for the relation between hypertension and both cognitive impairment and physical disability noted in other studies.[27,28]

The mechanisms of low vasoreactivity in hypertensive individuals are not fully understood. Our study suggests that there are ≥2 potential mechanisms that impair vasoreactivity in hypertension: one indirect mechanism via its relation with stroke and WMH, which eventually lower cerebral vasoreactivity,[29] and another independent of both. Hypertension is associated with significant decrease in NO production in the cerebral circulation,[30] and the ability of the cerebral circulation to respond appropriately to CO_2 is related to endothelial NO production.[31–34] Non-NO functions of the endothelium are also impaired in hypertension.[35] Adenosine-5′-triphosphate-dependent K+ channel activation may also mediate CO_2-induced NO activity in the pial arterioles.[36] Hypertension is also associated with structural changes in the blood vessels, such as increased tortuosity and reduced arteriolar branching, which may also affect cerebral vasoreactivity.[37]

Of particular concern is that vasoreactivity in stroke-free hypertensives is comparable to that of the stroke participants. This is of great significance, because from the cerebrovascular function perspective, the impact of hypertension is as severe as that of stroke. This suggests that hypertensive individuals without stroke have impaired cerebrovascular function comparable to those who already have stroke. Because impaired cerebrovascular reactivity to CO_2 is related to poor vascular and functional outcomes in various populations,[5,38] future studies that investigate the impact of antihypertensive medications on cerebral vasoreactivity are important.

Nondipping is associated with worse vascular macrovascular and microvascular brain injury in hypertension.[39,40] In this study we did not identify an association between dipping and cerebral vasoreactivity. The lack of association in this

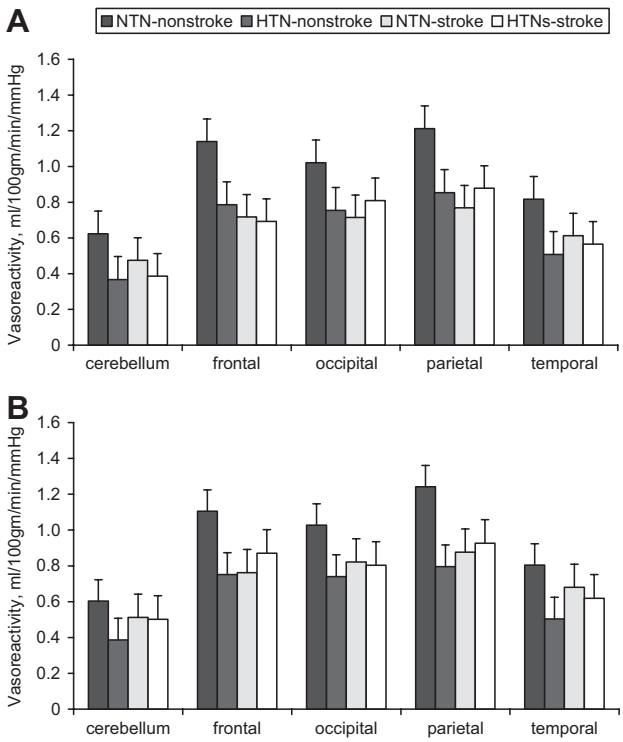

Figure 2. Regional cerebral vasoreactivity in stroke and nonstroke normotensive and hypertensive participants. A, Nonstroke side for the stroke participants and corresponding hemisphere in those without stroke. B, Stroke side for the stroke participants and the corresponding hemisphere in those without stroke. NTN indicates normotension; HTN, hypertension. Sample size: NTN, 22 (7 stroke and 15 nonstroke); HTN, 40 (23 stroke and 17 nonstroke). Values are least-square means adjusted for age, sex, body mass index, WMH/intracranial volume, and hypertensive therapy. In the nonstroke group, *P* value for the impact of hypertension on vasoreactivity was 0.035 and in the stroke group was 0.97 (stroke side) and 0.90 (opposite side).

study may be related to our relatively small sample size. It is also possible that nighttime dipping may not be intimately related to brain perfusion and cerebrovascular reactivity. We have reported previously that nocturnal dipping in blood pressure was not associated with global cerebral perfusion.[23]

Regionally, hypertension is related to lower vasoreactivity in all cortical regions. The magnitude of decrease in vasoreactivity from hypertension was greatest in the fornto-parietal regions. These 2 regions are involved in mood and in cognitive and physical performance.[41,42] We have reported recently that hypertensive individuals have impairments in mobility, cognition, and mood, even in the absence of clinical symptoms or disease.[43] This may shed more light on the possible mechanisms by which hypertension may be related to these impairments.

Although CASL-MRI is still not widely used clinically, this study provides evidence that it can be used to assess vasoreactivity. CASL-MRI requires no contrast. CASL-MRI also addresses previous limitations of TCD, has a relatively low signal:noise ratio, and, hence, is ideal to assess vasoreactivity in the brain.

One limitation of our study is the cross-sectional design, which precludes investigating the temporal relation between hypertension and vasoreactivity. As in most hypertension studies, antihypertensive exposure is an important confounder and limits our ability to study the natural impact of elevated blood pressure. In this study, we addressed this issue by performing our measures off antihypertensives, albeit only for few days for ethical reasons. We also adjusted all of our models for antihypertensive therapy.

Table 3. Adjusted Differences (±SE) in Vasoreactivity Between Hypertensives and Normotensive Participants by Brain Region and History of Stroke

Group	Region	Difference*	*P*
Nonstroke group	Cerebellum	0.22±0.16	0.18
	Frontal	0.35±0.16	0.03
	Occipital	0.29±0.16	0.08
	Parietal	0.45±0.16	0.007
	Temporal	0.3±0.16	0.07
Stroke group			
Stroke side	Cerebellum	0.09±0.16	0.57
	Frontal	0.02±0.16	0.87
	Occipital	−0.09±0.16	0.55
	Parietal	−0.11±0.16	0.49
	Temporal	0.05±0.16	0.76
Nonstroke side	Cerebellum	0.01±0.16	0.95
	Frontal	−0.11±0.16	0.51
	Occipital	0.02±0.16	0.91
	Parietal	−0.05±0.16	0.76
	Temporal	0.06±0.16	0.71

Model was adjusted for age, sex, body mass index, race/ethnicity, WMH/intracranial volume, and hypertensive therapy.

*Differences indicates least-square mean vasoreactivity in the normotensive group-hypertensive group. The differences between lobes were significant in all 3 of the groups ($P<0.001$ nonstroke group; $P=0.003$ stroke side; $P=0.005$ opposite side).

Conclusions

Hypertension is associated with low cerebrovascular reactivity to CO_2 independent of existing stroke or WMH. This decrease is similar in magnitude to that of stroke. Although all of the cortical regions are affected, the greatest impact was in the fronto-parietal region. Low vasoreactivity to CO_2 in hypertension may further increase the risk of developing brain-related end-organ damage, beyond its role in microvascular ischemic injury and macrovascular brain disease.

Perspectives

Hypertension is associated with significant impairment in cerebral vasoreactivity. This impairment is comparable to that from stroke. Because impaired cerebral vasoreactivity may be associated with poor functional and cognitive outcomes, prospective studies are needed to investigate the role of hypertension treatment in reversing these effects.

Sources of Funding

This analysis was supported by a National Institute on Aging grant (K23AG30057) to I.H. This study was supported by National Institutes of Health-National Institute on Aging grant 1R01-AG0287601A12, National Institutes of Health-National Institute of Neurological Disorders and Stroke grant R01-NS045745, and Na-

tional Institutes of Health-National Institute of Neurological Disorders and Stroke Small Business Technology Transfer grants 1R41NS053128-01A2, ADA1-06-CR-25, and UL1 RR025758 and M01-RR-01032 grants to V.N.

Disclosures

None.

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Online supplement: Hypertension and Cerebral Vasoreactivity: A Continuous Arterial Spin Labeling MRI study

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Cerebral perfusion was measured using Continuous Arterial Spin Labeling (CASL). CASL technology is non-invasive and uses proton labeling of the water molecules in the blood flowing in the blood vessels to allow for accurate and reproducible measures of perfusion.[3] It is sensitive to perfusion change and can be used for noninvasive mapping of cerebral blood flow ($ml \cdot 100g^{-1} \cdot min^{-1}$) and vasoreactivity to CO_2.[3-6] CASL images were acquired using a custom 3D stack of interleaved spirals fast spin echo sequence (T_R/ T_E = 6000/23.8 ms, Echo Train Length = 66, with a 18x18 cm FOV, in the coronal plane and 64 slices with thickness = 3.8 mm, 8 spiral interleaves, 2 averages and a bandwidth = ±62.5 kHz). Labeled and unlabeled images were collected over 2 minute periods during normal breathing, CO_2 rebreathing with 95% air and 5% CO_2 (hypercapnia), and hyperventilation (hypocapnia). Two scans were obtained during each phase and data was then averaged. Quantitative perfusion maps were reconstructed for each condition[6] (Research Systems, Boulder Co). Quantitative perfusion values were derived by segmenting the tissue into gray and white matter on the basis of the T1 maps and by using partition coefficients as described previously.[7] End-tidal CO_2 was continuously monitored and averaged over 15-second intervals. Blood pressure was measured in 1-minute intervals. Cerebral vasoreactivity was calculated as the slope of the regression between cerebral perfusion and end-tidal CO_2, in units of ml/100gm/min/mmHg, during normal breathing, CO_2 rebreathing, and hyperventilation. Perfusion was measured as the sum of both perfusion in the white and gray matter. We calculated a global cerebral vasoreactivity slope and regional vasoreactivity slopes in the frontal, parietal, temporal, occipital and cerebellar regions. In the stroke participants, vasoreactivity measures were calculated for both the stroke and non-stroke hemispheres. Except for the stratified analysis by stroke, we used the non-stroke hemisphere data in those with history of stroke for our analysis. There was a high correlation between the stroke hemisphere and non-stroke hemisphere vasoreactivity measures (correlation=88%, $p<0.001$).

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Table-S1: Adjusted regression coefficients and partial R^2 relating blood pressure (mean systolic and diastolic) and magnitude of nighttime dipping in systolic and diastolic blood pressure with global and regional CO_2 vasoreactivity

	Systolic blood pressure			Systolic blood pressure dipping		
Brain region	Beta* (SE)	Partial R^2	*p-value*	Beta* (SE)	Partial R^2	*p-Value*
Global Brain	-0.11(0.05)	0.16	*0.04*	-0.12(0.09)	0.06	*0.2*
Frontal Lobe	-0.11(0.06)	0.12	*0.05*	-0.15(0.11)	0.08	*0.16*
Parietal	-0.15(0.06)	0.18	*0.02*	-0.17(0.12)	0.07	*0.18*
Temporal	-0.08(0.05)	0.1	0.11	-0.1(0.08)	0.07	*0.2*
Occipital	-0.11(0.05)	0.16	*0.03*	-0.06(0.09)	0.02	*0.54*
Cerebellum	-0.09(0.04)	0.14	*0.05*	-0.03(0.08)	0.004	*0.74*
	Diastolic blood pressure			Diastolic blood pressure dipping		
Global Brain	-0.16(0.09)	0.11	0.08	-0.14(0.1)	0.07	*0.19*
Frontal Lobe	-0.13(0.1)	0.06	0.21	-0.17(0.12)	0.08	*0.16*
Parietal	-0.19(0.11)	0.1	0.11	-0.19(0.13)	0.08	*0.16*
Temporal	-0.13(0.08)	0.09	0.11	-0.13(0.09)	0.08	*0.14*
Occipital	-0.17(0.09)	0.13	0.06	-0.09(0.11)	0.03	*0.4*
Cerebellum	-0.18(0.07)	0.19	*0.02*	-0.05(0.09)	0.01	*0.58*

SE: Standard error. Adjusted for age, sex, race/ethnicity, body mass index, stroke, antihypertensives and white matter hyperintensities/intracranial cavity.
*Beta the regression coefficient of one unit of vasoreactivity per 10 mm of Hg of mean blood pressure or 10% of dipping from daytime to nighttime blood pressure

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