Longitudinal Changes in Cerebral Blood Flow in the Older Hypertensive Brain

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Background and Purpose—Changes in patterns of regional cerebral blood flow (rCBF) were assessed over a period of 6 years in 14 treated hypertensive participants (HTNs) and 14 age-matched healthy older participants (healthy controls [HCs]) in the Baltimore Longitudinal Study of Aging.

Methods—Resting-state PET scans collected at years 1, 3, 5, and 7 were used to determine differences in longitudinal patterns of rCBF change in HTNs relative to HCs. Pulse pressure, arterial pressure, systolic/diastolic blood pressure, and hypertension duration were also correlated with patterns of rCBF change in the HTN group.

Results—Relative to HCs, the HTN group shows greater rCBF decreases in prefrontal, anterior cingulate, and occipital areas over time, suggesting that these regions are more susceptible to hypertension-related dysfunction with advancing age. The HTN group also fails to show preservation of function over time in motor regions and in the temporal cortex and hippocampus as observed in HC. Although pulse pressure, mean arterial pressure, and systolic and diastolic pressure all correlate similarly with longitudinal rCBF changes, increased duration of hypertension is associated with decreased rCBF in prefrontal and anterior cingulate areas of functional vulnerability observed in the HTN group.

Conclusions—These results show that hypertension significantly affects resting brain function in older individuals and suggest that duration of hypertension contributes significantly to the patterns of change over time. (Stroke. 2007;38:1766-1773.)

Key Words: aging ◆ brain imaging ◆ hypertension
Aging medical examinations or the use of antihypertensive medications before participation in the neuroimaging study. During Baltimore Longitudinal Study of Aging visits, seated and standing morning blood pressure were measured from each arm by trained nursing staff using an appropriately sized cuff with mercury sphygmomanometer. Onset of hypertension was based on the first clinical diagnosis of the disease from Baltimore Longitudinal Study of Aging assessments or supplemental medical records. Participants who reverted to normotensive status without treatment were not included in these analyses.

Blood pressure on the day of the each PET session was assessed in a brief physical examination. Blood pressure was measured by a physician or physician’s assistant from the right arm using an appropriately sized cuff with mercury sphygmomanometer after the participant was resting in a seated position. These measurements were used to assess the relationship between blood pressure and cerebral blood flow in the PET scans.

Half (n=7) of the HTN subjects were medicated for hypertension at Y1 and the other half, although clinically diagnosed with hypertension by Y1, began medication at year 3 (Y3; n=4) or year 5 (Y5; n=3). Participants who began medication in Y3 or Y5 elected to adopt lifestyle and diet changes before resorting to treatment with antihypertensive drugs. The average duration of clinically diagnosed hypertension for the 14 participants was 9.1±4.9 years at Y1. Antihypertensive medications included diuretics alone (n=2), β-blockers with and without diuretics (n=5), calcium channel blockers with and without diuretics (n=3), and angiotensin converting enzyme inhibitors with and without diuretics (n=4).

PET Scanning
Participants underwent PET scans at baseline (Y1) and 6 annual follow-ups. Each session included a resting PET scan in which participants were instructed to keep their eyes open and focused on a computer screen covered by a black cloth. Participants also underwent PET scans during verbal and figural recognition memory. Scan order was counter-balanced but remained constant over repeated assessments. For compatibility with previous literature, we present analyses of the resting PET data.

PET measures of rCBF were obtained using [15O] water. For each scan, 75 mCi of [15O] water were injected as a bolus. Scans were performed on a GE 4096+ scanner, which provides 15 slices of 6.5-mm thickness. Images were acquired for 60 seconds from the time the total radioactivity counts in the brain reached threshold level. Attenuation correction was performed using a transmission scan acquired before the emission scans.

PET Data Analysis
The PET scans were realigned and spatially normalized into standard stereotactic space and smoothed to full width at half maximum of 12×12×12 mm in the x, y, and z planes. To control for variability in global flow, rCBF values at each voxel were ratio adjusted to the mean global flow of 50 mL per 100 g/min for each image. The image data were analyzed using Statistical Parametric Mapping (SPM2; Wellcome Department of Cognitive Neurology, London, England), where voxel by voxel comparisons determined significant changes in rCBF over time. Significant effects for each contrast were based on the magnitude of activation (t=3.03; P≤0.001) and spatial extent (200 mm3). To adjust for variations in the initiation of treatment in the HTN group, the results were covaried by the presence or absence of anti-hypertensive treatment during each year. All subjects had complete data for Y1, Y3, Y5, and Y7. Three different analyses were performed. First, longitudinal changes in resting rCBF were examined by comparing patterns at Y3, Y5, and Y7 to the Y1 baseline within the HC and HTN groups. To determine overall differences in longitudinal change between groups, the group by time interaction for change from Y1 to Y7 was examined. Conjunction analyses were then used to determine the direction of the effect (masking threshold P=0.05, magnitude P≤0.001, spatial extent >200 mm3). To ensure that rCBF changes were similar across individuals treated with different antihypertensive medications, individual rCBF values for regions showing group differences were extracted and plotted. Second, a linear regression was performed across Y1 to Y7 in each group to characterize regions that show steady progressive changes in blood flow and differences in longitudinal change between groups. Finally, to explain the differences in rCBF observed in the HTN group relative to HCs, correlation analyses were performed in the HTN group to examine the relationship between hypertensive characteristics and rCBF patterns. In separate analyses, pulse pressure, mean arterial pressure, systolic and diastolic blood pressure, controlled versus uncontrolled hypertension (binary analysis), and the duration of hypertension (total years after clinical diagnosis of hypertension with or without medication) were examined in relation to CBF patterns at Y1 and Y7. In each analysis, the individual values were entered as covariates for each scan and the effect of each covariate was examined.

Neuropsychological Testing
During each neuroimaging visit, participants completed a battery of 12 neuropsychological tests evaluating 6 cognitive domains. Memory was assessed using the California Verbal Learning Test and Benton Visual Retention Test. Word knowledge and verbal ability were measured using Primary Mental Abilities Vocabulary. Verbal fluency was assessed by letter and category fluency tests. Attention and working memory were measured by the Digit Span Test of the Wechsler Adult Intelligence Scale-Revised, and the Trail Making Test. Digits Backward, Trails B, and Verbal Fluency (categories and letters) assessed executive function. The Card Rotations Test assessed visuospatial function. Data from evaluations at Y1, Y3, Y5, and Y7 were used to examine differences in performance between the 2 groups.

Results
Hypertension
Although no HCs exhibited blood pressure >140/90 mm Hg at any point during the study, several of the HTN participants had elevated blood pressure levels (10 at Y1, 8 at Y3, 12 at Y5, 7 at Y9). Differences in blood pressure between the HC and HTN groups at Y1 to Y7 were analyzed using repeated measures ANOVA. There were overall effects of group for both systolic (t=7.04, df=26, P≤0.001) and diastolic (t=3.09, df=25, P=0.004) blood pressure levels, with significantly higher blood pressure levels in the HTN group throughout the study (HC Y1 =120/78 mm Hg, Y7 =125/72 mm Hg; HTN Y1 =144/84 mm Hg, Y7 =148/86 mm Hg; Figure 1). There was no overall effect of visit year and no significant group×visit interaction. The mean blood pressure for participants who began medication in Y3 or Y5 was 150/91±16/13 SD premedication and 148/84±16/7 SD postmedication. Mean blood pressure of participants who began medication before the imaging study was 137/81±16/9 SD at Y1.

Longitudinal Changes in rCBF
Age-related declines in rCBF were seen in the HC group from Y3 to Y7 relative to Y1 (Figure 2, second row). In Y3, the HC group showed declines in right-side superior prefrontal (Brodmann area [BA] 11), and superior (BA 22/42) and middle (BA 21/37) temporal cortices. Decreased activity was also seen in bilateral anterior cingulate (BA 32) and right posterior cingulate (BA 31) regions, and in the putamen and brainstem. In Y5, additional decreases were observed in left superior temporal (BA 38), bilateral insular, and left fusiform (BA 37) regions. Decreases were also noted in the right thalamus and cerebellum. In Y7, the HC group showed...
Figure 1. Longitudinal blood pressure levels. Means (SD) are shown for each group from Y1 to Y7. The HTN group had significantly higher blood pressure levels than HCs at each year (P<0.004). Overall mean across all years is also shown. The overall range of HC blood pressures was 76 to 138/50 to 80; the HTN group ranged from 105 to 182/60 to 106 across all years.

Additional age-related declines in bilateral medial (BA 9) and left inferior (BA 44) prefrontal, lingual (BA 18), and posterior cingulate (BA 31) regions (Table 1). Relative increases in flow over time were also observed in Y3 to Y7 relative to Y1 (Figure 2, bottom row). In Y3, increased rCBF was seen in left inferior (BA 10) and right middle (BA 10) prefrontal regions, the left postcentral (BA 4/43) and middle temporal (BA 37) gyrus, and in the right hippocampus and lingual gyrus (BA 19). In Y5, additional increases were observed in left superior (BA 10) and right inferior (BA 44) prefrontal regions, and in right precentral (BA 6) and cerebellar regions. In Y7 (Table 1), additional increases were noted in bilateral hippocampus, superior temporal (BA 22) and right middle occipital (BA 18) regions.

The HTN group exhibited a pattern of rCBF decline (Figure 2, top row) that included left-hemisphere anterior cingulate (BA 25), anterior temporal (BA 38), insular, lingual (BA 19), and right parahippocampal (BA 36) regions in Y3. In Y5, additional declines were seen in right superior temporal (BA 38), and left middle occipital (BA 19) and caudate areas. In Y7 (Table 1), additional declines were noted in right superior (BA 10), middle (BA 10), and medial (BA 9) prefrontal regions, bilateral superior temporal regions (BA 38), and left middle occipital and cuneus regions (BA 18/19). The HTN group also showed relative increases in flow over time (Figure 2, third row) in right superior (BA 10), bilateral middle (BA 9/10/46), and left inferior (BA 44) prefrontal regions; in bilateral middle (BA 21) and right inferior temporal (BA 20) cortices; and in right parahippocampal (BA 36), inferior parietal (BA 40), and middle occipital (BA 19) regions in Y3. In Y5, additional increases were observed in left medial (BA 11), right inferior prefrontal regions (BA 44), the right anterior cingulate gyrus (BA 25), left inferior temporal (BA 20), and cuneus (BA 18) regions. In Y7, an additional increase was noted in the left hippocampus (Table 1).

Although both groups showed longitudinal changes in rCBF over time, the primary analysis of group differences in longitudinal change from Y1 to Y7 revealed regions of greater longitudinal decline in HTN relative to HC (Figure 2, top right; Table 1). These declines appeared in middle and inferior prefrontal, anterior cingulate, occipitotemporal, and posterior occipital cortex. Individual rCBF values extracted within each of these regions showed a similar pattern of change across the antihypertensive drug classes. A linear analysis across Y1 to Y7 showed that these regions exhibit steady linear decreases across time in the HTN group (Figure 2, regions outlined in green; Table 2). In addition, the linear decline observed in most regions, with the exception of the right-side posterior occipital cortex, was greater in HTN than HC.

Group differences were also observed in the pattern of rCBF increase over time from Y1 to Y7 (Figure 2, bottom right; Table 1). Here, bilateral premotor (inferior frontal) cortex, superior temporal cortex, hippocampus, and left hemisphere primary motor cortex did not increase rCBF from Y1 to Y7 in the HTN group to the same extent as HCs. These regions, with the exception of the hippocampus and the right temporal regions, showed a linear increase in rCBF over time in the HTN group but this increase is significantly less than that observed in the HC group.

Effects of Hypertensive Variables on rCBF
The relationship between hypertensive characteristics and rCBF was examined in the HTN group alone (Figure 3). Almost identical blood flow maps were observed when comparing the relationship between pulse pressure, mean arterial pressure, systolic/diastolic blood pressure, and rCBF at Y7. For these variables, a negative correlation (increase in pressure related to decreased CBF) was observed in inferior frontal (BA 47), precentral (BA 6), middle temporal (BA 21), parahippocampal (BA 36), and fusiform (BA 19) gyri. When compared with Y1, these regions exhibited greater correlations at Y7, suggesting that the relationship between increased pressure and decreased rCBF becomes stronger over time. In the analysis of uncontrolled versus controlled hypertension, uncontrolled hypertension was related to greater declines in regions similar to those seen with the other blood pressure variables, with the exception of inferior frontal and temporal regions in the right hemisphere. Although these results demonstrated a significant relationship between various pressure levels and rCBF within the HTN group alone, they did not include the same regions that showed significantly different longitudinal change in the HTN group relative to HCs.

Duration of hypertension (9.1 ± 4.9 years at Y1) best explains some of the longitudinal changes in the HTN group, with more regions overlapping those that discriminate between HTN and HC than the other variables examined (Table 1). Overall, a negative relationship was observed between years of hypertension and CBF. Increased duration of hypertension was related to greater CBF decreases in many regions of the frontal lobe including superior (BA 10), middle (BA 10), and posterior (BA 11) cingulate.
9/11), medial (BA 10), and inferior (BA 10/45/47) prefrontal cortex. The precentral and postcentral (BA 6/43), anterior cingulate (BA 32), middle temporal (BA 21), parahippocampal (BA 36), and lingual gyri (BA 19) also showed a negative correlation with hypertension duration (Table 3). When compared with Y1, these regions exhibited greater correlations at Y7, suggesting the relationship between duration of hypertension and decreased rCBF becomes stronger over time.

Neuropsychological Performance

For each task or cognitive domain, a linear mixed model was used to determine task performance differences in the intercept (initial score) and slope (rate of change) between the

Figure 2. Longitudinal changes in cerebral blood flow. Changes in resting-state blood flow at Y3, Y5, and Y7 relative to Y1 baseline are shown for HTN (first and third panels) and HC (second and fourth panels) groups. Lateral and axial views of the brain are shown in each panel. Declines in rCBF are shown in blue and increases in are shown in red. Regions demonstrating linear changes in blood flow from Y1 to Y7 within each group are outlined in green. The images on the right show differences in longitudinal rCBF change between groups.
Our results show that hypertension affects resting brain function in older individuals. Both HC and HTN groups show

**Table 1. Linear rCBF Changes Over Time in Hypertension**

<table>
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<tr>
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<th>y</th>
<th>z</th>
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**Table 1. (Continued)**

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<td>Less rCBF increase in HTN vs HC</td>
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Local maxima within regions where rCBF differed at Y7 relative to Y1. Within-group changes and between-group differences are shown. Stereotaxic coordinates are listed, Brodmann areas are indicated in parentheses, t-values denote the magnitude of effect. Regions that overlap with rCBF patterns associated with systolic pressure, diastolic pressure, and blood pressure at time of scan, and duration of hypertension in the HTN group are noted.

HTN and HC groups. There were no significant differences in task performance between the groups on any measure for either initial score at Y1 or rates of change over time.

**Discussion**

Our results show that hypertension affects resting brain function in older individuals. Both HC and HTN groups show
longitudinal changes in CBF patterns, yet the pattern of change observed in the HTN group differs from HCs. Although pulse pressure, mean arterial pressure, systolic and diastolic blood pressure, and uncontrolled hypertension influence patterns of cerebral blood flow, the effect of hypertension duration best predicts the pattern of longitudinal change observed in the HTN group. Finally, although our PET results demonstrate altered functional brain changes over time in individuals with hypertension, a commensurate decline in cognitive function was not observed over the same interval in this otherwise healthy sample of hypertensive individuals.

PET Findings

Previous imaging studies have found functional differences in brain activity related to hypertension. During rest, both Mentis et al.7 and Fijishima et al.6 showed that individuals with treated hypertension exhibit decreased glucose metabolism and blood flow in the thalamus and striatum relative to healthy subjects. Jennings et al.5 found that parietal and occipitotemporal regions of the cortex showed decreased blood flow during verbal and spatial tasks in untreated hypertensive subjects.

Our results indicate that treated hypertension is associated with a longitudinal pattern of blood flow change that differs from healthy normotensive subjects. In healthy individuals, brain function changes with increasing age in a characteristic way. Changes in the patterns of brain activity, including both increased and decreased rCBF, are seen when comparing the older brain to the young brain12,13 and are observed over time in healthy older subjects as they age.14,15 In the present study, HTN is associated with greater longitudinal decline in middle and inferior prefrontal regions, the anterior cingulate gyrus, occipitotemporal regions, and in visual association cortices relative to HCs. Our HTN subjects also show regions where blood flow patterns do not indicate relative increases over time to the same extent as HC. These areas of relative reductions in CBF include primary motor cortex, superior temporal cortex, and the hippocampus. Further analysis revealed that most of these hypertension-related changes are linear in nature suggesting a slow steady progression of change over the 6-year follow-up.

Areas of substantially decreased rCBF in the HTN group likely represent regions of functional decline over time in association with hypertension. The implications of functional decline within these regions are far reaching, as prefrontal
dysfunction could influence memory\textsuperscript{16,17} and executive function.\textsuperscript{18,19} Anterior cingulate dysfunction can result in deficits in attention and error monitoring,\textsuperscript{20,21} and decreased activity in occipital and occipitotemporal cortices may impact visual perception and object recognition.\textsuperscript{22,23} Although our participants do not demonstrate significant cognitive decline presently, these decreases in flow suggest that hypertensives may be more susceptible than healthy individuals to dysfunction in the future with the onset of disease or other cardiovascular symptoms that could impair normal age-related compensatory mechanisms.\textsuperscript{12,24}

In our HC group, advancing age is associated with relative increases in frontal and temporal cortices and in the hippocampus. Although we did not measure absolute CBF because of the risk associated with repeated arterial blood catheterization, we interpret these increases as reflecting areas of preserved blood flow relative to age-related decreases in global blood flow.\textsuperscript{25,26} The HTN group shows reduced rCBF in these areas relative to the HC group, suggesting that the normal age-related preservation of activity in these regions is compromised in HTNs. Decreased preservation of function in the hippocampus suggests that medial temporal memory processes\textsuperscript{27,28} may also be compromised with long-term hypertension.

**Hypertensive Variables**

Our data show that pulse pressure, mean arterial pressure, and systolic and diastolic blood pressure all have a similar relationship to longitudinal patterns of CBF change in older individuals. These measures were inversely related with rCBF in the motor cortex, temporal association cortices, and the parahippocampal gyrus, indicating that higher pressure levels are associated with greater decreases in blood flow over time. These findings are significant in view of the involvement of the parahippocampal region in learning and memory\textsuperscript{29,30} and pathologic processes associated with dementia.\textsuperscript{31,32} and suggest that high pressure levels may lead to increased functional vulnerability of this brain region.

The regions showing correlations between CBF and measures of blood pressure are different from those showing greater longitudinal decline in the HTN compared with HC group. Duration of hypertension, however, is related to rCBF decreases not only in the parahippocampal gyrus but also in prefrontal cortex and the anterior cingulate gyrus, regions that show increased functional decline over time in the HTN group. This finding suggests that the most significant cumulative effects of hypertension on brain function are predominately attributable to the length of illness.

**Cognitive Function**

Hypertension is often associated with declines in cognitive function in older subjects. Deficits have been observed on tasks involving verbal\textsuperscript{33,34} and nonverbal\textsuperscript{33,35} memory, attention,\textsuperscript{36} executive function, and psychomotor speed.\textsuperscript{35,37} Our HTN subjects, however, do not demonstrate impairment in cognitive function relative to HCs. This may reflect the exceptional health status of the HTN subjects, and the exclusion of individuals with mild cognitive impairment and dementia as well as more severe cardiovascular disease. The lack of cognitive decline and impairment may also be caused by the small sample size and high functioning status of the Baltimore Longitudinal Study of Aging neuroimaging study participants, who are not representative of the general population in this regard. Nevertheless, our results indicate that rCBF changes are more sensitive to hypertension than cognitive measures in this sample.

**Conclusions**

Our findings of reduced rCBF in the occipitotemporal cortex support previous findings in individuals with hypertension.\textsuperscript{5} In addition, we showed that hypertension results in functional vulnerability of the prefrontal cortex, anterior cingulate gyrus, and hippocampus, regions implicated in memory, executive function, and attention. Although we found no concurrent cognitive impairments in the HTN group, this pattern of functional vulnerability may eventually foster accelerated cognitive decline relative to that observed in normotensive individuals.

These findings suggest that treated hypertension results in deleterious effects on brain function in the elderly. We cannot distinguish, however, between effects related to disease state and those related to treatment in this observational study. Our participants varied with respect to start of hypertension treatment and the types of medication used. Although examination of individual rCBF values suggests that participants treated with different drug classes show similar patterns of change over time, and although we attempted to control for the start of treatment in the HTN group in our analyses, the varied timing and regimens of treatment are a limitation of our study.

Another consideration is the adequacy of blood pressure control in the HTN group. Blood pressures varied across subjects, with 7 to 12 of the 14 HTNs remaining hypertensive in any given year of the study. This is not unusual in older individuals, as lowering blood pressure to normotensive levels is often difficult in the elderly.\textsuperscript{38} However, the patterns of rCBF change associated with high blood pressure does not fully explain the longitudinal rCBF patterns observed in the HTN group, suggesting that other factors play a larger role in these functional changes.

Additionally, the participants involved in this study were selected for excellent health other than presence of hypertension in the HTN group. The HTNs were specifically chosen to isolate the effects of hypertension without additional confounds associated with other cardiovascular risk factors. Although this group provides insight regarding long-term hypertension alone, the results may not generalize to individuals who have additional cardiovascular risk factors that may also influence brain function over time. Finally, these results are based on a relatively small sample of individuals. Although these limitations must be considered, our findings provide an initial examination of the effects of hypertension on longitudinal brain function.

**Acknowledgments**

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References
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