Brain Atrophy in Hypertension
A Volumetric Magnetic Resonance Imaging Study

Judith A. Salerno, Declan G.M. Murphy, Barry Horwitz, Charles DeCarli, James V. Haxby, Stanley I. Rapoport, and Mark B. Schapiro

To determine whether hypertension, the predominant risk factor for stroke and vascular dementia, is associated with brain atrophy, magnetic resonance imaging (MRI) scans were performed to quantify brain volumes and cerebrospinal fluid spaces. Eighteen otherwise healthy, cognitively normal older hypertensive men (mean±SD age, 69±8 years, duration of hypertension 10–35 years) and 17 age-matched healthy, normotensive male control subjects were studied in a cross-sectional design. Axial proton-density image slices were analyzed using region-of-interest and segmentation analyses. The hypertensive subjects had significantly larger mean volumes of the right and left lateral ventricles (p<0.05, both absolute volume and volume normalized to intracranial volume) and a significantly smaller normalized mean left hemisphere brain volume (p<0.05) with a trend toward significance for a smaller normalized mean right hemisphere volume (p<0.09). Four hypertensive subjects and one healthy control subject were found to have severe periventricular hyperintensities on T2-weighted MRI images. When data for these subjects were removed from the analyses, the normalized lateral ventricle volumes remained significantly larger in the hypertensive group. Lateral ventricle enlargement was not related to age or use of diuretics in the hypertensive group nor to duration of hypertension between 10 and 24 years. Our findings suggest that long-standing hypertension results in structural changes in the brain. Longitudinal studies will determine whether MRI-associated changes are progressive and if such changes identify hypertensive subjects at increased risk for clinically apparent brain dysfunction. (Hypertension 1992;20:340–348)

KEY WORDS • brain • magnetic resonance imaging • atrophy • hypertension, chronic • blood pressure • cerebral ventricles

Declines in US stroke mortality have been attributed to improved detection and treatment of hypertension. Nevertheless, hypertension remains the dominant risk factor for stroke and vascular dementia. Hypertension-associated changes in the cardiovascular and renal systems have been well described by clinical studies, using readily available, noninvasive techniques such as echocardiography or creatinine clearance calculated from 24-hour urine measurements. In vivo changes in the brains of hypertensive subjects are less commonly described, most likely because of fewer available methods for noninvasively studying the brain. In particular, there has been little emphasis on characterizing brain structure and function in hypertensive subjects in the absence of stroke or dementia.

With more widespread availability of structural imaging modalities such as computed x-ray tomography (CT) and magnetic resonance imaging (MRI), methods have been developed to not only describe, but also quantify structural changes in the brain associated with normal, healthy aging and with various pathological conditions such as Alzheimer's disease and Down's syndrome. However, there has been only one volumetric imaging study, using CT, that applied these techniques to hypertensive subjects. In that retrospective cross-sectional study, Hatazawa et al reported greater brain atrophy in older hypertensive subjects, including those with left ventricular hypertrophy, than in age-matched control subjects.

MRI offers advantages over CT for structural and quantitative brain imaging in that MRI does not use ionizing radiation, has no bone-hardening artifact, and has better spatial resolution. With appropriate analyses, MRI studies also can yield estimates of in vivo volumes of individual intracranial structures that are in close agreement with published volumes obtained from postmortem studies. Additionally, MRI is superior to CT in imaging white matter abnormalities in the brain, and the use of MRI has demonstrated a range of leukoencephalopathy previously not identified by CT.

White matter abnormalities are demonstrated in normal, healthy elderly individuals but are frequently associated with cerebrovascular risk factors, particularly hypertension. The clinical significance of these white matter abnormalities in asymptomatic persons remains controversial, but the abnormalities are thought by some to be caused by subcortical ischemic changes. Several MRI studies have correlated the presence of white matter changes in nondemented older hypertensive subjects with clinical characteristics such as blood pressure and neuropsychological test...
scores. White matter hyperintensities on MRI scans also have been shown to correlate with higher average 24-hour ambulatory blood pressures but not with office blood pressure measurements. Another study found no difference between neuropsychological test performance in older hypertensive individuals with or without white matter lesions on MRI scans, although CT evidence of white matter lesions—leukoaraiosis—has been implicated in dementia. Both of the above MRI studies used qualitative rating scales, and neither examined brain morphometrics. Whether loss of brain tissue accompanies white matter abnormalities has not been explored using CT or MRI.

This report compares MRI brain morphometrics in a group of otherwise healthy people with long-standing hypertension without known end-organ impairment and in healthy age- and sex-matched control subjects. Our purpose was to examine whether hypertension is associated with greater cerebral atrophy than is normal, healthy aging and whether disproportionate cerebral atrophy occurs in hypertensive individuals with severe white matter disease. An abstract of part of this work has been published.  

Methods

Subjects

Eighteen men and four women with established hypertension were initially examined. All were participants in an ongoing study of brain structure and function in hypertension at the Laboratory of Neurosciences of the National Institute on Aging. Subjects eligible for the study were at least 30 years old and had a history of hypertension that had been medically treated for more than 10 years. All were screened by history, physical examination, chest roentgenography, electrocardiography (ECG), and a battery of laboratory tests (complete blood count and sedimentation rate; concentrations of electrolytes, random glucose, blood urea nitrogen, creatinine, liver-associated enzymes, total cholesterol, and triglycerides; presence of antibodies to antinuclear antibodies; VDRL; presence of the human immunodeficiency virus; serum concentrations of vitamin B₁₂ and folate; tests of thyroid function; and urinalysis). No hypertensive subject had a significant medical, neurological, or psychiatric illness, a secondary cause of hypertension, or a disorder that might cause or contribute to brain dysfunction. Specifically, potential subjects were excluded if they had diabetes mellitus, renal dysfunction (including proteinuria), grade 3 or 4 retinal changes by the Keith-Wagener-Barber classification system, myocardial infarction, or cardiac dysrhythmias. One hypertensive subject had a right femoral artery bruit, but no other subject had evidence of peripheral atherosclerosis. Two hypertensive subjects initially had mildly elevated serum thyroid stimulating hormone levels (6.5 and 7.6 microunits/ml [normal range, 0.4–4.6 microunits/ml]) that were stable over a 3-year period (6.5 and 7.6 microunits/ml [normal range, 0.4–4.6 microunits/ml]) that were stable over a 3-year period. After the initial screening, subjects were also excluded for white matter lesions other than evident brain atrophy or white matter hyperintensities were noted on MRI or if the electroencephalogram (EEG) was abnormal. Once accepted into the study, subjects are seen at yearly clinic visits. Every 3 years, the subjects underwent brain MRI, high-resolution brain positron emission tomography, EEG, neuropsychological testing, 24-hour ambulatory blood pressure monitoring, and echocardiography. The study protocol was approved by our institutional review board, and informed consent was obtained from each subject.

Of the initial 22 hypertensive subjects, all four women were excluded because of an abnormal MRI scan or EEG or because they no longer required antihypertensive therapy. Eighteen hypertensive men with a mean±SD age of 69±8 (range, 51–80) years were studied (Table 1). Mean duration of hypertension was 16 (range, 10–35) years. Extensive medical records, dating back to the time of diagnosis and initiation of treatment and documenting adequate control of blood pressure (<140/90 mm Hg), were available on nine subjects. Incomplete records were available on the remaining subjects. All 18 hypertensive subjects were taking antihypertensive medication at the time of the MRI study; 10 were on a single drug regimen, seven were taking two drugs, and one took three antihypertensive medications (Table 2).

Seventeen age-matched male control subjects (mean±SD age, 69±7 years) also were studied. Each control subject underwent the same screening proce-

<table>
<thead>
<tr>
<th>Table 1. Subject Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
</tr>
<tr>
<td>Education (year)</td>
</tr>
<tr>
<td>Mini-Mental State Exam* score†</td>
</tr>
<tr>
<td>Duration of hypertension (year)</td>
</tr>
<tr>
<td>Clinic blood pressure measurements</td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
</tr>
<tr>
<td>Random, nonfasting serum concentions</td>
</tr>
<tr>
<td>Sodium (mmol/l)</td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
</tr>
</tbody>
</table>

Values are mean±SD. All subjects were male. *p<0.05 different from control. †Normal score, >24.

<table>
<thead>
<tr>
<th>Table 2. Antihypertensive Medications at Time of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
</tr>
<tr>
<td>Single-drug therapy</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitor</td>
</tr>
<tr>
<td>β-Blocker</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
</tr>
<tr>
<td>Diuretic</td>
</tr>
<tr>
<td>Multiple-drug therapy</td>
</tr>
<tr>
<td>Diuretic + other drug</td>
</tr>
<tr>
<td>Other combination</td>
</tr>
</tbody>
</table>

*Seven subjects on two-drug regimen, one subject taking three medications.
were higher than those of the control group (Table 1).

The hypertensive group had a significantly lower mean serum potassium than the control group (Table 1).

Of laboratory studies obtained at the initial screening, their mean clinic systolic and diastolic blood pressures were lower than any control subject. The hypertensive subject with a significantly lower level of education between the groups (Table 1) because of one subject at the initial clinic evaluation; however, between the groups when that hypertensive subject was removed from the analysis.

Seventeen of the 18 hypertensive subjects and 16 of the 17 control subjects were right-handed.

There was a significant difference in mean level of education (eighth grade) than any control subject. The hypertensive subject had a significantly lower level of education because of one subject at the initial clinic evaluation; however, between the groups when that hypertensive subject was removed from the analysis.

All hypertensive and control subjects scored within normal ranges on screening tests of cognitive function, including the Folstein Mini-Mental State Examination and the Blessed Dementia Scale. Each subject had a Hachinski ischemia score of 2 or below. Once accepted into the study, after a 2-week medication washout period each subject also underwent an extensive neuropsychological evaluation that confirmed the finding of cognitive normality (Table 3; see below). A medication washout period was implemented for all subjects because of evidence that antihypertensive therapy may influence cognitive performance. A daily blood pressure measurement was obtained on each hypertensive subject during the washout period; no subject had sustained blood pressure elevations of greater than 200 mm Hg systolic or 115 mm Hg diastolic. All subjects, however, remained hypertensive for the majority of the washout period, and each returned to his usual antihypertensive regimen after completion of the neuropsychological testing.

There was a significant difference in mean level of education between the groups (Table 1) because of one hypertensive subject with a significantly lower level of education (eighth grade) than any control subject. The mean level of educational achievement was not different between the groups when that hypertensive subject was removed from the analysis.

All hypertensive subjects were taking antihypertensive medications at the initial clinic evaluation; however, their mean clinic systolic and diastolic blood pressures were higher than those of the control group (Table 1). Of laboratory studies obtained at the initial screening, the hypertensive group had a significantly lower mean serum potassium than the control group (Table 1). Seventeen of the 18 hypertensive subjects and 16 of the 17 control subjects were right-handed.

Magnetic Resonance Imaging

MRI studies of the brain were performed using a 0.5-T scanner (Picker Corp., Cleveland, Ohio). Thirty-six 7-mm-thick contiguous slices oriented parallel to the inferior orbitomeatal line were obtained. Eighteen axial slices were quantitatively analyzed using the proton density (resonance time [TR], 2,000 msec; echo time [TE], 20 msec) portion of a double-echo sequence (TR, 2,000 msec; TE, 20/80 msec) with 192 views and two repetitions. The MRI data were stored in digital form on magnetic tape and were analyzed on a VAX 750 computer (Digital Equipment Corp., Maynard, Mass.) using a Gould 8400 image array processor (Gould Inc., Fremont, Calif.). MRI evaluations of hypertensive and control subjects were interspersed over a 3-year period.

Analytical Methods

Two previously described methods were used to determine the volumes of specific brain structures; region of interest (ROI) analysis was applied to determine the volumes of the cerebrum, the cerebral hemispheres, and several subcortical nuclei and segmentation analysis was used to determine the volumes of the total cerebrospinal fluid (CSF) space and of the cerebral brain matter (see below). Peripheral CSF volume was calculated by subtracting the ventricular CSF volume obtained by ROI analysis from the total CSF volume determined by segmentation analysis. Volumes were expressed as percentages of the total traced intracranial volume to control for the differential effect of individual head size and height. All volumetric analyses were performed by the same operator, a physician with expertise in brain imaging analysis. Intrarater and interrater reliabilities, however, were determined for all brain ROIs traced as part of this analysis. Highly significant intrarater and interrater reliabilities were obtained for all ROIs (p<0.01). Qualitative ratings of periventricular hyperintensity (PVH) and deep white matter hyperintensity (DWMH) also were conducted on the T2-weighted images of the MRI study.

Region of interest analysis. In the ROI analysis, the operator traced the total intracranial volume and then outlined each cerebral hemisphere (brain matter plus CSF space) separately by following the dura along the inner table of the skull. The medial surfaces of the cerebral hemispheres were bisected by following the dura into the interhemispheric fissure and then drawing a straight line connecting the anterior and posterior interhemispheric fissures. ROIs were traced by visual inspection on each axial image on which they were present, from the vertex to the foramen magnum. The subcortical nuclei were traced after using a histogram equalization method to enhance the contrast between gray and white matter. The number of enclosed pixels was determined for an outlined ROI in a given slice. The net ROI volume (in cubic centimeters) was calculated by multiplying the summed pixel areas (each pixel, 1 mm²) by the slice thickness (7 mm). For a structure that appeared on more than one slice, the volumes derived from each slice were added to obtain a total volume.

Segmentation analysis. To obtain measures of CSF and brain matter volumes on each slice, a semiautomated method of analysis was used, based on MRI pixel...
The Porteus Maze Test** provided a measure of planning and foresight.**

**Derived volumes.** Peripheral CSF volumes were calculated by subtracting the sum of the tracked ventricular CSF volumes from the CSF volumes obtained by segmentation analysis (e.g., right peripheral CSF volume=right hemisphere CSF volume-right lateral ventricular volume—third ventricular volume). In addition, volumes of the caudate, lenticular, and thalamic nuclei (right plus left) were divided by the total cerebral brain matter volume to determine if disproportionate atrophy occurred in the subcortical nuclei compared with the cerebral hemispheric brain matter.

**Qualitative ratings.** White matter hyperintensities visible on T2-weighted MRI images were qualitatively rated. A three-point rating scale, adopted from Fazekas et al., was used to assess the extent of the white matter changes. PVH was rated as 0, absent; 1, caps or pencil thinning; 2, smooth halo around the lateral ventricles; and 3, irregular PVH extending into the deep white matter. DWMH was graded as 0, absent; 1, punctate foci (single or multiple); 2, minimal confluence of foci; and 3, large confluent areas. Each MRI scan was independently rated by two physicians blinded to the patient’s identity and diagnosis. Interrater reliability was high (κ=0.80, p<0.01 for PVH; κ=0.64, p<0.01 for DWMH). White matter abnormalities were considered severe if the average rating was 1.5 or greater. Because ratings never differed by more than one grade between raters, a mean score of at least 1.5 meant that one or both observers rated the white matter changes as grade 2. Because of motion artifact that obscured the white matter, the MRI scan of one control subject was not rated.

**Neuropsychological Tests**

In addition to the screening tests of cognitive function, each subject was administered a battery of neuropsychological tests after a 2-week washout period of all prescribed and over-the-counter medications. The overall measure of cognitive function was the Wechsler Adult Intelligence Scale (WAIS). The WAIS intelligence quotient was divided into verbal and performance scores. Factor deviation quotients from the WAIS tested the verbal fund of knowledge (Verbal Comprehension), visuospatial construction (Perceptual Organization), and immediate verbal memory span and calculation ability (Memory and Freedom From Distractibility). Visuospatial construction was also measured using the Extended Range Drawing Test. Immediate memory for visuospatial location was measured with the Block Tapping Span Test. An additional test of language function, the Controlled Word Association, or FAS test of verbal fluency,** also was administered. Attention to a simple set was measured by Trail A of the Trailmaking Test, and attention to a complex, shifting set was measured by Trail B. The Porteus Maze Test provided a measure of planning and foresight.

---

**Table 4. Absolute Volumes of Intracranial Structures and CSF Spaces as Measured by Magnetic Resonance Imaging**

<table>
<thead>
<tr>
<th>Volume (cm³)</th>
<th>Control</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total intracranial volume</td>
<td>1,404±160</td>
<td>1,453±278</td>
</tr>
<tr>
<td>R hemisphere*</td>
<td>619±65</td>
<td>634±120</td>
</tr>
<tr>
<td>L hemisphere*</td>
<td>621±63</td>
<td>638±129</td>
</tr>
<tr>
<td>Total cerebral brain matter</td>
<td>1,083±131</td>
<td>1,109±232</td>
</tr>
<tr>
<td>R hemisphere brain matter</td>
<td>545±58</td>
<td>553±112</td>
</tr>
<tr>
<td>L hemisphere brain matter</td>
<td>544±61</td>
<td>548±117</td>
</tr>
<tr>
<td>R thalamus</td>
<td>7.3±0.7</td>
<td>7.7±1.6</td>
</tr>
<tr>
<td>L thalamus</td>
<td>7.4±0.8</td>
<td>7.7±1.5</td>
</tr>
<tr>
<td>R lenticular nucleus</td>
<td>6.9±1.4</td>
<td>7.7±2.4</td>
</tr>
<tr>
<td>L lenticular nucleus</td>
<td>6.6±1.5</td>
<td>7.9±2.6</td>
</tr>
<tr>
<td>R caudate</td>
<td>5.1±1.0</td>
<td>5.8±1.6</td>
</tr>
<tr>
<td>L caudate</td>
<td>5.4±0.8</td>
<td>6.1±1.8</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; R, right; L, left; SEM, standard error of the mean. Values are mean±SD.

*Brain matter and CSF

†p<0.05, ‡p<0.01 different from control (Student's t test).

**Statistics**

The cerebral volumes (absolute values and volumes normalized to the total intracranial volume), neuropsychological test scores, and MRI white matter ratings were compared between groups using Student’s unpaired t test. For the hypertensive group, the relations between age and ventricular volume and between duration of hypertension and ventricular volume were analyzed by linear regression. Relations between the hypertensive group’s neuropsychological test scores and the right and left lateral ventricle sizes were compared using Spearman’s method of correlational analysis. The χ² statistic was used to evaluate whether there was an association between hypertension and the presence of severe white matter hyperintensities. Statistical significance was defined as p<0.05 for all analyses.

**Results**

Mean (absolute) volumes of the cerebral structures and spaces are presented in Table 4. Only the right and left lateral ventricle volumes differed significantly between groups; the right lateral ventricle volume in the hypertensive group was 56% larger than that in the control group, the left 86% larger. Because the hypertensive group had a larger total intracranial volume than the control group (although the difference was not
significant), data normalized to the total intracranial volume were further analyzed (Table 5). Normalization of structural imaging data has been used to reduce the variability associated with intrasubject differences in height and head size.\textsuperscript{14,47} Mean normalized volumes of the right and left hemisphere ROIs, which include both CSF and brain matter, did not differ between the groups. However, when CSF volumes were subtracted from hemispheric volumes, the hypertensive group had a significantly smaller mean left hemisphere brain matter volume than the control group. The mean right hemisphere brain matter volume also was smaller, but the difference failed to reach the level of significance (\(p<0.09\)).

There was no significant difference between groups in mean normalized volume of any subcortical nucleus (Table 5). Because of relatively greater atrophy of the subcortical nuclei compared with the cerebral brain matter in normal, healthy aging,\textsuperscript{14} ratios of subcortical nuclei volumes to total cerebral brain matter volume also were compared; there was no significant difference between the groups on any of these measures.

Comparison of normalized CSF space volumes between the groups are shown in Table 6. Mean volumes of both the right and left lateral ventricles, but not of the third ventricle, were significantly larger in the hypertensive subjects. This finding is illustrated in Figure 1. Whereas the hypertensive subjects had numerically larger volumes of all CSF measurements, neither total, right or left hemisphere, nor peripheral (subarachnoid) CSF volumes differed significantly from control values (\(p>0.05\)).

There was no association between hypertension and the presence of white matter hyperintensities (by \(\chi^2\)
Table 7. Periventricular and Deep White Matter
Hyperintensities—Qualitative Ratings

<table>
<thead>
<tr>
<th>Rating</th>
<th>Periventricular hyperintensities</th>
<th>Deep white matter hyperintensities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (n=16)</td>
<td>Hypertensive (n=18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control (n=16)</td>
</tr>
<tr>
<td>0</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Mean±SD rating</td>
<td>0.8±0.6</td>
<td>0.9±0.9</td>
</tr>
</tbody>
</table>

Values are number of subjects unless noted.

test, p>0.05), and the hypertensive group did not have more severe mean PVH or DWMH ratings than the control group (Table 7). However, because it is technically difficult using the histogram-equalization process, to outline the subcortical nuclei when periventricular white matter changes are present (D. Murphy, unpublished observation), t test comparisons were repeated after data for all subjects with severe periventricular changes were removed. Of the previously significant findings, the difference between the groups' mean left hemisphere brain matter volumes was weaker but remained close to the level of significance (p<0.058). The findings of larger right and left lateral ventricle volumes in the hypertensive group remained significant. In addition, to control for a possible effect of diuretics on CSF production rate,49 the mean lateral ventricle volume of hypertensive subjects on single or combination diuretic therapy (n=10) was compared with that of the remaining hypertensive subjects; no significant difference was found. There were no differences in white matter ratings between those subjects on diuretics and the other hypertensive subjects.

There was no significant linear relation between lateral ventricle volume and age in either the hypertensive (Figure 2) or the control group. Duration of hypertension, however, was related significantly to both right

![Figure 2](https://hyper.ahajournals.org/content/59/4/345.full)

**Figure 2. Scatterplot shows results of linear regression of right (*) and left (△) lateral ventricle volume as function of hypertensive subjects' age. Correlations were not significant. Similarly, age was unrelated to ventricle size in healthy control subjects (not shown).**

(r=0.63) and left (r=0.67) ventricle volume (Figure 3). However, when data for the one hypertensive subject who had been treated for hypertension for 35 years was removed from the analysis, the relations were no longer significant. In all cases for which adequate past medical records were available, initiation of treatment of hypertension began at the time of diagnosis or followed within 1 year.

There was no significant difference between the hypertensive and control groups in mean score on any neuropsychological test (Table 3). All individuals scored within the normal ranges. In addition, there was no significant correlation between volumes of the right and left lateral ventricles and any neuropsychological test score.

**Discussion**

Using quantitative MRI volumetric analysis, we found significant lateral ventricular enlargement and left hemisphere brain matter atrophy in older, medically treated hypertensive men compared with sex- and age-matched control subjects. These results confirm and extend the previous findings, using CT, of Hatazawa et al.18 which demonstrated brain atrophy in older hyper-
tensive subjects. In contrast to our study, however, that study was retrospective and the authors selected hypertensive subjects who met voltage criteria for left ventricular hypertrophy on their electrocardiograms. Additionally, those authors did not indicate which hypertensive subjects received antihypertensive therapy before the study, nor was the duration of hypertension diagnosis or treatment in each subject known. In contrast, we selected subjects for whom medical treatment was documented for at least 10 years. Only one of our 18 hypertensive subjects and none of our control subjects had left ventricular hypertrophy by ECG voltage criteria (echocardiograms to confirm this finding are currently being performed on all subjects). Thus, our hypertensive subjects most likely were healthier than those in the study of Hatazawa et al. Despite differences in subject selection criteria, imaging modalities, and methodologies, our findings are similar to those of Hatazawa et al. Thus, we conclude that even with adequate treatment of elevated blood pressure, hypertensive subjects show morphological changes in brain structure.

Results of previous studies on hypertensive rats (SHR) have parallels to the current findings. Ritter and Dinh reported progressive dilatation of cerebral ventricles in SHR, beginning at 4 weeks of age, compared with Wistar-Kyoto (WKY) and Sprague-Dawley normotensive rats. A later study found that reduction of blood pressure with an angiotensin converting enzyme inhibitor, beginning in utero and continuing throughout the life of the SHR, failed to attenuate the ventricular dilatation. Also, SHR were found to have smaller total brain masses and volumes than normotensive WKY rats. Our findings confirm that treatment of hypertension does not reduce mean ventricular size to normal, although an additional comparison with untreated hypertensive subjects may provide further information on the extent of cerebral ventricle dilatation.

Whereas white matter hyperintensities on MRI can occur in normal healthy elderly persons, the incidence and severity of the hyperintensities are higher in the presence of cerebrovascular risk factors, notably hypertension. Our laboratory recently showed that systolic blood pressure levels correlated with the severity of white matter changes, as measured by a qualitative rating scale, in older subjects with normal-range blood pressures. The same qualitative scale was used in the present study to distinguish the severity of an individual's white matter changes on MRI scans. Because of potential measurement artifacts due to severe white matter changes, we repeated t test analyses using data for only those subjects who did not have severe periventricular white matter disease. The finding of larger normalized lateral ventricle volumes in the hypertensive group remained significant but the finding of a smaller normalized left hemisphere brain matter volume did not (p = 0.058), suggesting a small role for severe white matter disease as a contributing factor in brain atrophy. This is consistent with observations in older persons of decreased attenuation in CT-imaged white matter in association with brain atrophy and of frontal periventricular white matter lucencies associated with increased ventricular size.

Because some post mortem studies have reported increased extracellular water as a concomitant of MRI white matter changes before death, we reanalyzed our data excluding those subjects taking diuretics to control for possible effects of diuretics on water content in the brain. Diuretics are known to alter CSF production rate. We reasoned that the effect, if present, would be most evident in the periventricular regions. After excluding data for those subjects taking diuretics from the analyses, the findings did not change, because of the nonsignificance of a diuretic effect.

Increased cortical atrophy and lateral ventricle dilatation, as well as severe white matter disease, have been associated in neuroimaging studies with cognitive dysfunction. The neuropsychological test results from the present study demonstrate, however, that our hypertensive subjects were cognitively normal. Additionally, there was no relation between neuropsychological test scores and atrophy measures. Although we selected for subjects who were cognitively normal, individual subjects with atrophy, if sufficiently progressive, eventually may be at risk for developing vascular dementia. To date, no subject has become demented; however, since some of the MRI scans and neuropsychological testing one subject has had a left hemisphere intracranial hemorrhage and two others have developed symptomatic coronary artery disease.

We estimated the duration of hypertension by review of past medical records. For half of our subjects, including several with extensive military or employment medical records, we could confirm the dates of onset, diagnosis, and initiation of treatment of hypertension. For the remaining subjects, records that were available but did not extend back to the time of diagnosis were reviewed. Linear regression analysis showed that lateral ventricular enlargement was related significantly to duration of hypertension (and duration of treatment) but not to age (Figures 2 and 3). The significance of the relation was due, however, to one outlier with a long duration of hypertension (35 years) that exceeded that of all other subjects by more than 10 years. The relation between duration of hypertension and lateral ventricular enlargement will remain uncertain until subjects with durations of hypertension between 24 and 35 years are studied.

The most robust finding of this study was enlargement of the lateral ventricles by more than 50% in the hypertensive group. However, total CSF volume, to which the normalized lateral ventricle volume contributes about 15%, was not significantly enlarged. In addition, the normalized left hemisphere brain matter volume showed significant atrophy, whereas the difference in right hemisphere volume approached the level of statistical significance. These findings suggest that ventricular dilatation is greater than cortical atrophy. Proportionately more cortical atrophy than ventricular dilatation has been found with CT in neurodegenerative conditions such as Alzheimer's disease. In hypertension, however, such changes may reflect the distribution of the underlying pathophysiology. For example, changes may occur earlier or more extensively in the deep white matter of hypertensive subjects because of pathological alterations of small vessels and arterial border zones. Hypertension and its reactive arteriopathy may predispose to progressive decreases in cerebral blood flow and lead to chronic ischemic states and tissue loss. This could occur independently of medical
treatment, or it could possibly be exacerbated by antihypertensive medications. However, if MRI white matter abnormalities are assumed to be ischemic in nature, our finding of ventricular enlargement in the absence of severe white matter changes might argue against a vascular hypothesis. Alternatively, alterations in CSF dynamics or in cerebrovascular permeability may predispose to ventricular dilatation, although these hypotheses were not testable in the current study.

In conclusion, in a cross-sectional study, older, medically treated hypertensive men who were cognitively normal were found to have larger mean right and left lateral ventricular volumes when their MRI scans were compared with those of age-matched healthy men. This result was independent of the presence of severe white matter hyperintensities. Additionally, the hypertensive subjects were found to have left hemisphere brain matter atrophy when volumes were normalized to the total intracranial volume. These findings occurred in the absence of apparent end-organ involvement and despite verifiable antihypertensive therapy. The long-term consequences of these clinically silent structural changes in hypertension will need to be determined by longitudinal studies.

References
7. Devereux RB, Savage DD, Sachs I, Laragh JH: Relation of hemodynamic load to left ventricular hypertrophy and performance in hypertension. Am J Cardiol 1983;51:171–176
14. Murphy D, DeCarli C, Schapiro M, Rapoport SI, Horwitz B: The effects of healthy aging on volumes of the subcortical nuclei, brain matter, and cerebrospinal fluid in males as measured with MRI. Arch Neurol (in press)
55. Awad IA, Johnson PC, Spetzler RF, Hodak JA: Incidental subcortical lesions identified on magnetic resonance imaging in the elderly: II. Postmortem pathological correlations. Stroke 1986;17:1090–1097
Brain atrophy in hypertension. A volumetric magnetic resonance imaging study.
J A Salerno, D G Murphy, B Horwitz, C DeCarli, J V Haxby, S I Rapoport and M B Schapiro