Hypertension Correlates With Lenticulostriate Arteries Visualized by 7T Magnetic Resonance Angiography


Abstract—Hypertension, a major risk factor for stroke, is associated with altered arterial anatomy and function; however, the limited resolution of current imaging techniques has restricted the in vivo study of microvascular changes in the brain. In this report, we quantitatively examined the lenticulostriate arteries in hypertensive patients using ultrahigh-field 7T MRI. We compared the number of stems and branches, curvature, and tortuosity of the lenticulostriate arteries by 3D time-of-flight magnetic resonance angiography among 20 hypertensive patients (mean age: 46.6±9.1 years) and 20 age-matched healthy subjects (mean age: 47.7±8.1 years). The average numbers of stems and branches in hypertensive patients were significantly less than those of healthy subjects \( (P<0.002) \). However, this difference was abolished in older volunteers (>45 years old), whereas the difference between young hypertensive patients (≤45 years old) and age-matched healthy controls was augmented by 55% for stems and 91% for branches \( (P=0.001) \). In comparison, there were no differences in the average curvature and tortuosity of the lenticulostriate arteries and no significant difference when corrected for smoking \( (P=0.064) \). In conclusion, our results showed that there was a substantial difference in the lenticulostriate arteries of hypertensive patients compared with healthy individuals when observed in vivo by ultrahigh-resolution 7T magnetic resonance angiography, and the difference was considerable in young subjects. \( (\text{Hypertension. 2009; 54:1050-1056.}) \)

Key Words: microvessels ■ hypertension ■ magnetic resonance angiography ■ 7T MRI ■ lenticulostriate arteries

Hypertension is considered to be one of the most important risk factors for strokes, heart attacks, heart failure, and arterial aneurysms. Hypertension can promote and/or be induced by changes in the small arterial and arteriolar architecture via vascular hypertrophy, endothelial dysregulation, and atherosclerosis. These structural changes disturb the microcirculation, resulting in high vascular resistance and reduced blood flow through the microvessels. Given the relatively high blood flow through the anterior cerebral artery and middle cerebral artery, hypertensive patients have a particularly high incidence of stroke. Their perforators, the lenticulostriate arteries (LSAs), play a major role, because lacunar infarcts account for >20% of all strokes, and 35% to 44% of intracerebral hemorrhages involve the basal ganglia. This is because the blood supplied to these territories comes from end arteries that have little or no collateral circulation. Moreover, hypertension is associated with >70% of all intracerebral hemorrhages and lacunar infarcts, as well as white matter changes and silent strokes. Thus, imaging of the LSAs in vivo could offer important insight for understanding the mechanisms of microvascular diseases associated with hypertension.

Although current neuroimaging techniques, including magnetic resonance angiography (MRA), computed tomographic angiography, and digital subtraction angiography, have been used to investigate vascular pathophysiology, the study of microvascular diseases in vivo has been restricted by their inherent invasiveness and/or limited resolution. Recently we succeeded in the noninvasive, in vivo imaging of cerebral microvessels, like the LSAs, using ultrahigh-field MRI, such as 7T. In our previous studies, we only examined the microvasculature of healthy subjects.

On the basis of previous studies and our own, we have hypothesized that direct visualization of the LSAs using 7T MRA could possibly reveal subtle changes in the cerebral microvasculature associated with hypertension. In this study, we report our findings on the structural differences between the LSAs of hypertensive patients and healthy subjects by the quantitative analysis of LSA images obtained by 7T MRA.

Materials and Methods

Subjects and MR Protocols

Twenty recently diagnosed hypertensive patients who had taken no antihypertensive medications until this study and 20 healthy volunteers as age-matched controls, whose ages ranged from 31 to 72 years old (mean±SD: 46.6±9.1 for patients and 47.7±8.1 for controls), were enrolled in this study. Informed consent was obtained for each of the 40 participants, who all were of Korean decent. The
Table. Demographic Comparison of Hypertensive Patients With Healthy Controls

<table>
<thead>
<tr>
<th>Category</th>
<th>Healthy Subjects</th>
<th>Hypertensive Patients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>47.7±8.1</td>
<td>46.6±9.1</td>
<td>0.702</td>
</tr>
<tr>
<td>Systolic BP/diastolic BP, mm Hg</td>
<td>113.3±7.2/73.5±4.8</td>
<td>153.6±16.4/103.5±12.2</td>
<td>&lt;0.001*/&lt;0.001*</td>
</tr>
<tr>
<td>MAP, mm Hg†</td>
<td>86.8±4.9</td>
<td>120.2±11.4</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>BT, °C</td>
<td>36.2±0.4</td>
<td>36.3±0.4</td>
<td>0.399</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>66.8±7.5</td>
<td>71.6±9.5</td>
<td>0.96</td>
</tr>
<tr>
<td>No. of stems</td>
<td>7.1±1.6</td>
<td>5.6±0.9</td>
<td>0.001*</td>
</tr>
<tr>
<td>No. of branches‡</td>
<td>11.2±2.2</td>
<td>8.9±2.2</td>
<td>0.002*</td>
</tr>
<tr>
<td>Curvature, °§</td>
<td>724.4±168.8</td>
<td>768.3±207.3</td>
<td>0.467</td>
</tr>
<tr>
<td>Tortuosity§</td>
<td>1.5±0.1</td>
<td>1.5±0.2</td>
<td>0.555</td>
</tr>
</tbody>
</table>

MAP indicates mean arterial pressure; BT, body temperature; HR, heart rate. *P<0.05. †MAP is diastolic pressure + (systolic pressure – diastolic pressure)/3. ‡Data show only branches that are originated from the stems of the LSAs. §This was calculated from data of the 2 largest branches of the LSAs in each hemisphere.

The study protocol was approved by the university institutional review board and the Korean Food and Drug Administration.

Imaging of the LSAs was conducted with 7T MRI (Magnetom, Siemens AG). The MRA parameters used in this study were the same as those described in our previous reports.9,10 For the purpose of identifying any abnormal brain lesions, we used a conventional 1.5T MRI. Before imaging the target vessels, that is, the LSAs, we conducted lower-resolution MRA imaging with an isotropic voxel size of 0.8 mm and an acquisition time of 1 minute and 42 seconds, respectively. Using a mercury-filled sphygmomanometer, and each measurement was performed at least twice for each reading, as described in a previous report.11

For imaging the LSAs, we used a birdcage type radiofrequency coil specifically designed for angiographic applications with 7T MRI. Before imaging the target vessels, that is, the LSAs, we conducted lower-resolution MRA imaging with an isotropic voxel size of 0.8 mm and an acquisition time of 1 minute and 42 seconds, which provided us with the scout images for LSA imaging, as well as information for determining large vessel abnormalities. For the visualization of the acquired 3D MRA data, the maximum intensity projection of the region of interest was made by focusing on the main trunk of the middle cerebral artery, as well as the anterior cerebral artery to center the LSAs.

Data Analysis

We examined the major large vessels, including the middle cerebral artery, anterior cerebral artery, posterior cerebral artery, and internal carotid artery, of hypertensive patients and healthy subjects using low-resolution MRA data to determine the presence of vascular structural abnormalities, such as stenosis or aneurysms. The microvascular structures of the LSAs were analyzed quantitatively on the basis of morphological characteristics (branches, stems, tortuosity, and curvature) between hypertensive and nonhypertensive subjects with respect to the following factors: age, smoking, alcohol consumption, severity of hypertension (stage I and II hypertension as defined by the seventh report of Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure),11 and systolic and diastolic hypertension.

Stems were defined as the portion of the LSAs that originated directly from the middle cerebral artery or anterior cerebral artery, as described previously.13 Branches were defined as daughter vessels originating from common stems of parent LSAs plus stems without any branches (single vessels). Only the blood vessels pointing toward the anterior perforated substances were counted.

We also measured the angle, length, and curvature of each LSA on 2D maximum intensity projection images using routines based on MATLAB (The MathWorks). The schematic in Figure 1A demonstrates the method used for measuring the length and angle of the LSAs. The symbols in the formula, $\Delta\phi$ and $l(n)$, indicate the angle of the segmented vessels ($\sim1$ to 2 mm per segment) with respect to the vertical axis and the length of the segmented vessels, respectively. Representative examples of a healthy subject and a hypertensive patient are shown in Figure 1B and 1C, respectively. Using the acquired data, we calculated the LSA curvature and tortuosity using methods described previously.14 Curvature was calculated using data from the 2 most prominent LSAs of each hemisphere, in which ≥2 branches were found. The data processing was performed by 2 trained technicians who were blinded to the status of the subjects, and the results were analyzed independently by the authors.

Statistical Tests

Differences between the mean values of the hypertensive and nonhypertensive groups were analyzed using the Student’s (independent) t test. The 2 groups were further subdivided into smoking versus nonsmoking groups and young (<45 years old) versus old (>45 years old) groups and analyzed using independent t tests. Interobserver variability between the 2 readers who counted the LSA branches and stems was assessed by the Spearman’s ρ correlation coefficient. Statistical significance was defined as $P<0.05$. All of the statistical analysis was carried out with SPSS 15.0 (SPSS Inc).

Results

First, we examined the trunks and bifurcations of the large vessels for abnormalities, including stenotic vessels and cerebral aneurysms, using low-resolution scout images with 7T MRI. Aside from normal individual variations, we found no evidence of vascular abnormalities in both patients and healthy controls, as shown in Figure 2A and 2B, respectively.
Figure 3 shows images of 2 representative LSAs obtained from hypertensive patients (Figure 3A) and age-matched healthy subjects (Figure 3B) using 7T MRA. On gross observation, these images show a substantial decrease in the number of LSA stems and branches of hypertensive patients compared with healthy controls. Subsequent quantitative line tracings of the LSAs corresponding with Figure 3A and 3B are shown in Figure 3C and 3D, respectively, which were drawn to clearly distinguish the LSA characteristics for analysis.

The pairwise comparison of the number of LSA stems and branches yielded no statistically significant difference between the 2 readers, indicating a similar appraisal (Spearman’s $\rho$: 0.521 and 0.716 at a confidence level of $P<0.016$ and $P<0.001$ for stems and branches, respectively). Figure 4A shows the mean number of stems and branches of LSAs for both patients and healthy controls. The average numbers of stems and branches in hypertensive patients ($5.6 \pm 0.9$ and $8.9 \pm 2.2$) were $\approx 73.2\%$ and $74.2\%$ of that in the control group, respectively ($7.1 \pm 1.6$ and $11.2 \pm 2.2$; $P<0.002$). The average curvature and tortuosity of the LSAs of hypertensive patients, however, were only $5.7\%$ ($768.3$ versus $724.4$) and $2.0\%$ ($1.49$ versus $1.46$) higher than those of the control subjects.

Figure 1. Methodology for measuring the length, curvature, and tortuosity of the LSAs. A, A schematic illustration of the measurement of LSAs parameters. B, and C, Representative 7T MRA images of the LSAs, their tracings, and measured values for normal and hypertensive subjects, respectively.

Figure 2. Large major cerebral arteries from 3 representative hypertensive patients and controls obtained with 7T MRI. Three axial maximum-intensity projection images obtained by low-resolution time-of-flight MRA of hypertensive patients (A) and healthy control subjects (B).
group, respectively, and these differences were not statistically significant.

To determine whether smoking exacerbates the observed effect of hypertension on the LSAs, we compared the number of stems and branches of smokers and nonsmokers within the hypertensive group, as shown in Figure 4B. There was no difference in the number of stems between the 2 groups, and although nonsmokers had slightly more branches than smokers, this finding was not significant (P = 0.064). Differences in the LSA count were not related to alcohol consumption (P = 0.18), nor did these finding change when analyzed with respect to systolic or diastolic hypertension individually or severity of hypertension (data not shown).

We examined the effect of aging on the LSA microvasculature by subdividing the hypertensive and nonhypertensive subjects into 2 groups: younger individuals ≤45 years old and older individuals >45 years old. As shown in Figure 5A, the young hypertensive group had fewer LSA stems and branches than their age-matched healthy controls (P < 0.005 and P < 0.001, respectively), whereas the older group (Figure 5B) showed no significant difference compared with age-matched healthy subjects (stems: P < 0.13; branches: P < 0.4). The difference between normotensive and hypertensive individuals within the young subgroup compared with the difference for the total population was 55% greater for stems (2.3 versus 1.5) and 91% greater for branches (4.4 versus 2.3).

Discussion

In the present study, we examined 7T MRA images of the LSAs of subjects with hypertension and compared them with age-matched healthy subjects. We found that the LSAs between healthy controls and hypertensive patients were noticeably distinct, as seen in Figure 3 and quantified in Figures 4 and 5. Even by direct observation, the numbers of visible stems and branches in the hypertensive patients appear substantially less. There are several possible explanations for this finding. First, small vessels may have been difficult to visualize angiographically because of a decrease in signal intensity attributed to reduced blood flow through the microvessels caused by an increase in peripheral vascular resistance and/or structural changes in the LSAs associated with hypertension. In addition to reduced flow, the diameter (normally between 80 and 1400 μm; mean: 472 μm) of a number of the LSAs in the hypertensive group may be below the imaging resolution (<230 μm) of 7T MRI. This comparison seems reasonable, because pathological and in

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**Figure 3.** 7T MRA images of the LSAs of hypertensive patients vs those of age-matched healthy subjects. Two representative LSA images of hypertensive patients (A) obtained with 7T MRA alongside age-matched healthy subjects (B). The numbers at top left corner of each image indicate the age and BP of the subjects. C and D, Corresponding line tracings of the LSAs of patients and healthy subjects shown in A and B, respectively. Stems are labeled with Roman numerals, whereas branches are labeled with Arabic numerals. *Data show perforators that were not counted because of their unclear origin. Note that the sum of the uncounted branches in the entire healthy control group was more than that of hypertensive patients (51 vs 40).
vivo retinal data showing arterial luminal narrowing associated with hypertension support this finding. Many studies have indirectly investigated the effects of hypertension on the cerebral microvasculature by observing changes in the retinal vessels, because these microvascular systems share many regulatory processes. They showed that the diameter of the retinal arteries was indirectly correlated with the incidence and development of hypertension.16,17

Second, the absolute number of LSA vessels may be reduced, because hypertension is known to induce microvascular rarefaction, a reduction in the number of small arteries and capillaries. However, evidence supporting this phenomenon in the brain has been unclear.18,19 There may be other factors that influence the signal intensity of MRA images, such as intracranial pressure, and additional factors that disturb cerebral blood flow, which were outside the scope of this study.

We also found that the difference in the mean value of observable stems and branches of the LSAs between hypertensive and normotensive individuals was abolished with age. As shown in Figure 5A, there was a significant difference in the number of stems and branches of the LSAs between hypertensive patients and healthy subjects equal to or younger than 45 years of age. However, the lack of difference in the older group (>45 years old), as shown in Figure 5B, might be because of other factors that affect the vascular morphology independent of hypertension. Studies have shown that the density of the cerebral microvasculature decreases with age,20 whereas retinal artery studies have shown that the vessel diameter decreased by 4.8 mm for every decade after 60 years of age, independent of the effects of hypertension.21 However, because of our small sample size, larger studies will be needed to confirm these results.

Smoking has a direct relation with the incidence of cardiovascular disease and stroke.22 On that account, we investigated the effects of smoking on cerebral microvasculature. Comparison of smokers and nonsmokers among the hypertensive patients showed a small but not statistically significant difference in the number of branches. Moreover, we found no difference in the number of stems. Our findings suggest that smoking may not play a large role in the ability to visualize the LSAs; however, more subjects will be needed in future studies to determine whether smoking affects the hypertension-associated reduction in the observable LSA count.

Many studies have found a significant relationship between vascular structural changes, such as vascular tortuosity, and hypertension.23,24 However, this correlation is still a matter of controversy.25 Although the representative LSA images shown in Figure 3 seem to indicate that there are differences in the tortuosity and curvature between hypertensive patients and controls, in the present study we could not find quanti-
tative evidence to support this relationship. This may be because of limitations in the method used to measure these morphological differences, or there may be, in fact, no relation between them. This issue should be further investigated. Other factors, such as serum levels of low-density lipoprotein, high-density lipoprotein, fibrinogen, and diabetes mellitus, were not addressed in the current study; however, further studies should be performed to determine their contribution to changes in the LSAs.

As shown in Figure 2, MRA data acquired with resolutions commonly used in clinics could not provide any information regarding the microvascular status of the subjects. However, microvascular imaging could provide important clinical information on the early detection and/or response to treatment of cerebrovascular-related diseases. Our data suggest that hypertension has an effect on the microvasculature, particularly that of younger individuals. Therefore, it may be important to closely follow this group, because the prevalence of lacunae dramatically increases immediately after 45 years of age. Preliminary data in Figure 6 show evidence of microvascular changes as a result of antihypertensive medication in relatively young patients. Although limited subjects were evaluated in this trial, the effects of antihypertensive drugs on the morphology of the cerebral microvasculature as visualized by 7T MRA merit further consideration as to the importance of this contribution.26,27

In conclusion, we have expanded on previous studies using ultrahigh-resolution magnetic resonance angiographic imaging of the LSAs to investigate how reliably one can differentiate hypertensive patients from healthy subjects. By taking advantage of the ability to directly visualize microvascular structures in vivo, this study provides additional evidence for a direct relationship between cerebral microvascular changes and hypertension.

Perspectives
The present report demonstrates that the proposed technique could be used to observe various physiological changes and pathological processes related to cerebral microvascular diseases, such as aging and stroke, in the human brain in vivo.28 With future long-term follow-up studies, this technique may provide important clues to the early detection of individuals who are at high risk for small vessel diseases and lacunar stroke, particularly among hypertensive patients and the elderly population.29

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Disclosures
None.

References


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