Evaluation of Cerebral Vasoreactivity by Three-dimensional Time-of-Flight Magnetic Resonance Angiography

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Background and Purpose  
Cerebral vasoreactivity is an important indicator of the reserve capacity of the cerebral circulation. To make a quantitative analysis of cerebral vasoreactivity in individual major arterial territories, we evaluated the response to acetazolamide using three-dimensional time-of-flight magnetic resonance angiography.

Methods  
We examined 10 healthy volunteers and 6 patients with unilateral stenosis of the middle cerebral artery by a 1.5-T superconducting magnetic resonance imaging system. After a baseline vascular image was obtained, each subject received 17 mg/kg IV of acetazolamide; a second scan was performed 20 minutes later. Using a generally available personal computer and image analysis software, we measured the areas of the individual major arteries on collapsed axial vascular images and then calculated the vasoreactivity.

Results  
The average vasoreactivity of individual major cerebral arterial territories in the healthy volunteers was as follows: anterior cerebral artery complex, 33%; right middle cerebral artery, 71%; left middle cerebral artery, 74%; right posterior cerebral artery, 68%; and left posterior cerebral artery, 68%. In the patient group, the vasoreactivity of the stenotic middle cerebral arteries was significantly smaller than that of the nonstenotic arteries (P<.05). In addition, the nonstenotic middle cerebral arteries showed significantly less vasoreactivity than the right arteries of the healthy volunteers (P<.01).

Conclusions  
Three-dimensional time-of-flight magnetic resonance angiography can be used to quantitatively evaluate acetazolamide-induced vasoreactivity in individual major cerebral arterial territories. (Stroke. 1994;25:1807-1811.)

Key Words  
acetazolamide • angioigraphy, magnetic resonance • cerebral blood flow • cerebral arteries

Acetazolamide (Diamox) is known to increase cerebral blood flow and has been used for assessment of the reserve capacity of the cerebral circulation in patients with ischemic cerebrovascular disease. If the capacity for cerebral autoregulation is exhausted, the response to acetazolamide is reduced or absent. Cerebral vasoreactivity, an indicator of autoregulatory reserve capacity, has been assessed by the 133Xe inhalation system,22 stable xenon computed tomography,4-5 or single-photon emission computed tomography (SPECT) with 133Xe.6 123I-labeled isopropylidopaamphetamine,7 or 99mTc-labeled hexamethylpropyleneamine oxime.8-10 Doppler sonography has also been used to detect an increase in flow velocity induced by acetazolamide11-13 and carbon dioxide.14-16 However, to our knowledge, evaluation of cerebral vasoreactivity with three-dimensional time-of-flight magnetic resonance angiography (3D TOF MRA) has never been reported.

Our previous study17 compared the vascular images obtained by 3D TOF MRA before and after acetazolamide administration and indicated that this drug improves the visualization of small peripheral arteries that are not depicted on the baseline image. Our findings also raised the possibility of assessing vasoreactivity with 3D TOF MRA and acetazolamide. Accordingly, the present study was designed quantitatively to evaluate acetazolamide-induced vasoreactivity in individual major cerebral arterial territories by 3D TOF MRA.

Subjects and Methods

Subjects  
We investigated 10 healthy volunteers (7 men and 3 women; age, 28 to 76 years [mean, 51 years]) as well as 6 male patients in the chronic stage of ischemic cerebrovascular disease (age, 50 to 74 years [mean, 59 years]). Conventional cerebral angiography revealed that each patient had a single stenotic lesion located in the middle cerebral artery (MCA).

MR Studies  
Magnetic resonance (MR) studies were performed by a 1.5-T superconducting MR imaging system using a head coil and commercially available software (SIGNA ADVANTAGE, General Electric Medical Systems). Vascular MR imaging was performed with a 3D TOF technique. Images were obtained with spoiled GRASS (gradient-recalled acquisition in the steady state) sequence, which had a repetition time of 34 milliseconds, a system-selected echo time of 4.3 milliseconds, two excitations, a 20-degree flip angle, a 128x256 matrix, an 18-cm field of view, and a 60-mm excitation volume divided into 60 axial partitions. The frequency encoding direction was anteroposterior. "Flow compensation" and "no phase wrap" settings were used for the vascular scans. The center of the
target volume was placed slightly above the circle of Willis. Immediately after a baseline MR angiogram was obtained, each subject received 17 mg/kg IV acetazolamide (Diamox; Lederle Japan Ltd). Twenty minutes later, MR angiography was repeated under the same conditions as the baseline study. From each set of data, collapsed axial angiographic images were created by use of a standard maximum intensity projection algorithm, and then the images were produced on a scale of 3.3 cm to each 5 cm of the actual brain.

Image Processing

The collapsed axial angiographic images were scanned with an image scanner at 144 pixels per inch of its setting. The graphic data thus obtained were processed to determine the cerebral vasoreactivity with a generally available personal computer and image analysis software (Fig 1). At first, from the aspect of difference in signal intensity between the arteries and the background, arterial signals were extracted from the collapsed axial images and were defined as the whole arterial tree. On these images, the anterior cerebral artery (ACA), MCA, and posterior cerebral artery (PCA) were identified. Because the roots of the MCA and ACA were overlapped by the internal carotid artery in the axial view, the obscured portions were excluded from assessment. These manipulations were performed under the same conditions for paired baseline and postacetazolamide images. Because the bilateral ACAs could not be separated from each other in the axial view, we estimated ACA vasoreactivity with combined data for both arteries (the ACA complex). Then the area of the whole arterial tree and the areas of the ACA complex, MCAs, and PCAs were measured in terms of pixel counts.

Calculation of Vasoreactivity

From these data, the acetazolamide-induced vasoreactivity of the whole arterial tree and the individual major arteries were calculated as follows:

\[
\text{Vasoreactivity (\%) = 100 \times \left( \frac{\text{Area After Acetazolamide}}{\text{Area Before Acetazolamide}} - 1 \right) }
\]

Statistical Analysis

The significance of differences between the mean values of unpaired data was assessed with the Mann-Whitney U test, and differences between paired data were assessed with the Wilcoxon matched-pairs signed rank test. The vasoreactivity versus age relation in normal volunteers was evaluated by simple linear regression analysis. Probability values of \( P < .05 \) were regarded as statistically significant.

Results

There were no serious adverse effects of acetazolamide administration, although one subject complained of minor side effects including facial numbness and dizziness. Approximately 45 minutes was required for the series of MR examinations to be completed, and approximately 30 minutes per subject was required for data processing to determine the vasoreactivity.

None of the major arteries were outside the target volume on the sagittal projection images in our series of MR angiograms, and the estimation of vasoreactivity could be performed in all subjects.

The acetazolamide-induced vasoreactivity of the normal volunteers is shown in Table 1, and that of the patients is shown in Table 2.

In the normal volunteers, the mean values for the right and left MCA were 71% and 74%, respectively, while the bilateral PCA had the same value of 68%. The ACA complex and the whole arterial tree showed reactivities of 33% and 52%, respectively. There were no significant differences in the mean values between the right and left MCAs or PCAs.

In the patient group, the mean responses of the MCA (Fig 2A) and PCA (Fig 2B) were significantly smaller than those in the normal volunteers, not only on the side with MCA stenosis but also on the contralateral side. In addition, the mean response of the stenotic MCA was significantly smaller than that of the nonstenotic MCA (\( P < .05 \)) (Table 2, Fig 2A). The mean response of the PCA ipsilateral to the side of MCA stenosis was also smaller, although not significantly, than that of the contralateral PCA (Table 2, Fig 2B).

Linear regression analysis of the relations between age and the vasoreactivity of the whole arterial tree, the ACA complex, the right MCA, the left MCA, the right PCA, or the left PCA showed no significant correlation in the normal volunteers.

Discussion

The present study showed that 3D TOF MRA could detect the acetazolamide-induced increase of arterial area and could quantitatively evaluate the vasoreactivity of individual major cerebral arterial territories on the basis of a series of MR angiograms.

The advantages of this method are as follows: (1) The vasoreactivity of individual major cerebral arterial territories can be assessed in one series of MR examinations; (2) vascular images can be obtained in addition to quantifying the cerebral vasoreactivity; and (3) the method is less invasive or noninvasive and safe. We were able to determine the vasoreactivity of individual major arterial territories in patients with unilateral MCA stenosis. It is pathophysiologically interesting to estimate the vasoreactivity of each major arterial territory in patients with ischemic cerebrovascular disease.

In most previous studies of cerebral vasoreactivity, it has been estimated by the \( ^{133} \text{Xe} \) inhalation system, SPECT, or transcranial Doppler sonography (TCD), but none of these methods permits vascular imaging. Our recent study of 3D TOF MRA\(^ {17} \) revealed that acetazolamide administration made it possible to detect small peripheral arteries that were not depicted on baseline images. In addition, acetazolamide administration improved the sensitivity of detecting stenotic lesions in the main trunks of the major cerebral arteries and decreased the false-positive diagnosis of occlusion in these arteries. Besides permitting such precise vascular imaging, 3D TOF MRA with acetazolamide also allows the estimation of cerebral vasoreactivity as shown in the present study. It is the only noninvasive method available that simultaneously provides vascular images and measures cerebral vasoreactivity. Contrast angiography\(^ {18} \) could provide the same information, although it is invasive. The vasoreactivity of major cerebral arteries can also be estimated by TCD, but usually this method cannot determine the vasoreactivity of the bilateral MCAs and PCAs at one examination.

Acetazolamide increases cerebral blood flow immediately after intravenous administration\(^ {11,19} \) and is believed to cause the dilatation of precapillary arterioles by inhibition of carbonic anhydrase. There have been no previous reports on the effect of acetazolamide on the diameter of the major cerebral arteries. The vasoreactivity that was assessed in this study was probably related to an increase of cerebral blood flow and flow velocity in the vessels examined, induced by
the drug. Such effects increased the proportion of unsaturated spins in a section, and consequently the peripheral arteries whose signal intensities were too low to be detected before acetazolamide administration might be made visible by the drug. Thus, 3D TOF MRA allowed us to assess acetazolamide-in-
duced vasoreactivity as the percent increase in cerebral blood flow.

It is reported that the regional cerebral blood flow of normal volunteers increases an average of 1.3-fold to 1.7-fold after the intravenous administration of acetazolamide,2-6,11,12 and our results were in agreement with these previous studies.

Our method also has some disadvantages. Since vasoreactivity is assessed by projecting the vascular images in an axial plane, some errors may be unavoidable. In particular, the reactivities of ACA might be underestimated. On the axial view, the root of ACA and its distal portions are overlapped. Consequently, even if the distal portions are made visible by acetazolamide, the effect portions are overlapped. Consequently, even if the distal portions are made visible by acetazolamide, the effect cannot be estimated on the view. However, the error would probably be constant in a subject, and therefore our method may be more suitable for long-term follow-up of patients and for assessment of the response to medical or surgical treatment. The vessel whose area is smaller than a pixel may be measured larger than its actual area. This overestimation, however, may be subtle and can be reduced by using a larger matrix size (eg, 512x512) or a smaller field of view.

Højér-Pedersen3 reported that patients with unilateral occlusion of a major cerebral artery showed a smaller response to acetazolamide in the symptomatic hemisphere than in the asymptomatic hemisphere. Using TCD, Karnik et al13 showed that the acetazolamide-induced increase of mean blood flow velocity in the

### Table 1. Acetazolamide-Induced Cerebral Vasoreactivity in Healthy Volunteers

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age, y</th>
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<th>L MCA</th>
<th>R PCA</th>
<th>L PCA</th>
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<tr>
<td>1</td>
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<td>28</td>
<td>13.7</td>
<td>26.9</td>
<td>16.1</td>
<td>39.1</td>
<td>34.2</td>
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<tr>
<td>2</td>
<td>M</td>
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<td>71.5</td>
<td>33.9</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
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<td>33.8</td>
<td>79.9</td>
<td>62.4</td>
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<td>74.1</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
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<td>39.6</td>
<td>72.7</td>
<td>76.1</td>
<td>52.6</td>
<td>115</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>43</td>
<td>60.2</td>
<td>84.8</td>
<td>83.2</td>
<td>125</td>
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</tr>
<tr>
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<td>F</td>
<td>52</td>
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<td>39.5</td>
<td>8.3</td>
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<td>103</td>
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<td>F</td>
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<td>34.1</td>
<td>52.9</td>
<td>52.1</td>
<td>60.5</td>
<td>44.9</td>
</tr>
</tbody>
</table>

Mean 51.1 33.1 70.7 73.8 67.8 67.9 52.2

SD 16.6 10.6 22.7 31.9 33.3 33.3 31.5

ACA indicates anterior cerebral artery complex; MCA, middle cerebral artery; PCA, posterior cerebral artery; Whole, whole arterial tree; R, right; and L, left. Vasoreactivity data are shown as percentages.

### Table 2. Acetazolamide-Induced Cerebral Vasoreactivity in Patients With Unilateral Middle Cerebral Artery Stenosis

<table>
<thead>
<tr>
<th>Case</th>
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<th>C-MCA</th>
<th>S-PCA</th>
<th>C-PCA</th>
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<td>11</td>
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<td>M</td>
<td>55</td>
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<td>M</td>
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<td>M</td>
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<td>32.2</td>
</tr>
<tr>
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<td>M</td>
<td>63</td>
<td>22.7</td>
<td>27.9</td>
<td>25.0</td>
<td>13.6</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>74</td>
<td>32.0</td>
<td>37.9</td>
<td>43.0</td>
<td>57.7</td>
</tr>
</tbody>
</table>

Mean 59.0 25.3* 33.8 25.2 30.6

SD 8.4 8.8 13.9 13.8 20.4

MCA indicates middle cerebral artery; PCA, posterior cerebral artery; S, ipsilateral to the stenotic MCA, and C, contralateral to the stenotic MCA. Vasoreactivity data are shown as percentages. *P<.01 vs C-MCA (Wilcoxon matched-pairs signed rank test).
MCA was smaller on the affected side than on the contralateral side in patients with unilateral internal carotid artery occlusion. In contrast, Vorstrup et al\textsuperscript{30} reported that cerebral blood flow in the MCA territory and the mean flow velocity in the MCA increased to approximately the same degree on the occluded and nonoccluded sides after acetazolamide administration in patients with common carotid artery occlusion. Yamashita et al\textsuperscript{8} and Maeda et al\textsuperscript{9} reported, in patients with MCA stenosis and internal carotid artery obstruction, respectively, that cerebral reserve capacity on the contralateral side was decreased, although not significantly, compared with non-cerebrovascular accident control subjects. In contrast, Levine et al\textsuperscript{11} reported by positron emission tomography that, in patients with unilateral carotid distribution ischemia, cerebral perfusion reserve was significantly decreased in both the ischemic and nonischemic sides compared with control subjects. The present study in which we used 3D TOF MRA clearly showed that the vasoreactivity of the stenotic artery was significantly smaller than that of the nonstenotic artery in patients with unilateral MCA stenosis and that even the vasoreactivity of the nonstenotic MCA was significantly smaller than that of the right MCA in healthy volunteers.

Bonte et al\textsuperscript{12} examined healthy volunteers for possible age and sex differences in the response to acetazolamide using SPECT and reported no such differences. Piepras et al\textsuperscript{13} found no significant correlation between age and the acetazolamide-induced increase of MCA blood flow velocity measured by TCD in healthy subjects. In patients with ischemic cerebrovascular disease, it was reported that the vasodilatory response to acetazolamide did not change with age.\textsuperscript{9} Although our linear regression analysis involved a small number of subjects, it agreed with these reports.

We conclude that 3D TOF MRA combined with acetazolamide administration is potentially clinically useful because it not only provides accurate vascular images but also allows assessment of the vasoreactivity of individual major cerebral arterial territories. However, further investigation is needed to compare the response to acetazolamide obtained by 3D TOF MRA with that obtained by previous methods, such as the \textsuperscript{133}Xe inhalation system, SPECT, and TCD.

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