Acetazolamide challenge for three-dimensional time-of-flight MR angiography of the brain.

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Acetazolamide Challenge for Three-Dimensional Time-of-Flight MR Angiography of the Brain

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PURPOSE: We compared three-dimensional time-of-flight MR angiograms obtained before and after acetazolamide administration to evaluate whether use of this drug could improve visualization of small peripheral intracranial arteries and atherosclerotic stenosis. **METHODS:** For evaluation of small peripheral arteries, 10 patients with clinical diagnosis of ischemic cerebrovascular disease and 10 healthy volunteers were investigated, and for evaluation of stenosis, another 6 patients were investigated. Vascular images were obtained by three-dimensional time-of-flight MR angiography. After a baseline scan, 17 mg/kg acetazolamide was injected intravenously and the second scan was performed 20 minutes later. **RESULTS:** Several small peripheral arteries that had not been seen on the baseline images were visible on the acetazolamide images without any augmentation of the background signals. Stenotic lesions in the main trunks of the major cerebral arteries were detected more clearly on acetazolamide images. **CONCLUSIONS:** Acetazolamide improves visualization of small peripheral intracranial arteries and sensitivity in detecting atherosclerotic stenosis in the main trunk of major cerebral artery by three-dimensional time-of-flight MR angiography without changing MR apparatus and software.

Index terms: Magnetic resonance angiography (MRA); Angiography, contrast media; Atherosclerosis

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Magnetic resonance (MR) angiography is a noninvasive procedure for evaluating vascular abnormalities. However, small peripheral intracranial arteries are not clearly visible by MR angiography, and atherosclerotic stenosis of the major intracranial arteries cannot be delineated as accurately with MR angiography as with conventional cerebral angiography (1).

Acetazolamide is easy to administer, safe, and inexpensive, and it induces vasodilation with a rapid increase in cerebral blood flow after intravenous injection. The exact mechanism by which the drug causes vasodilation is unclear, but it is believed to be mediated by inhibition of carbonic anhydrase. Inhibition of carbonic anhydrase increases arterial carbon dioxide tension and may cause the cerebral vasodilation and accompanying augmentation of cerebral blood flow (2–6).

To evaluate the hypothesis that intravenous acetazolamide administration would improve the visualization of small peripheral intracranial arteries and atherosclerotic stenosis by three-dimensional time-of-flight MR angiography, we compared MR angiograms obtained before and after the administration of this drug.

Methods

Subjects

We investigated 16 patients with ischemic cerebrovascular disease and 10 healthy volunteers.

To evaluate the acetazolamide-induced visualization of the peripheral artery, we investigated 10 patients (all men) ranging in age from 48 to 77 years (mean, 64) with clinical diagnosis of ischemic cerebrovascular disease; their major cerebral arteries were not stenotic nor occluded (except in one case). The 10 healthy volunteers (7 men and 3 women)

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TABLE 1: Visualization of small cerebral arteries in healthy subjects and patients with cerebrovascular disease

Healthy	Case 1[a]		Case 2		Case 3		Case 4		Case 5		Case 6		Case 7		Case 8		Case 9		Case 10		Mean	
	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
R-angular	2	3	2	3	2	2	2	3	2	3	2	3	2	2	2	3	2	3	1	2	1.9	2.7
L-angular	2	2	2	3	2	3	2	2	2	2	2	3	2	3	2	2	2	3	2	3	2.0	2.6
R-insular	2	3	2	3	2	3	2	3	1	2	2	2	2	3	2	3	2	3	2	3	1.9	2.8
L-insular	2	3	2	3	1	2	2	2	1	2	2	2	1	1	2	3	2	3	1	2	1.6	2.3
R-P.com	1	1	3	3	2	3	2	2	2	2	2	2	2	2	1	1	1	1	2	2	1.8	1.9
L-P.com	1	1	1	1	2	3	2	2	1	1	1	1	3	3	1	1	1	1	2	2	1.5	1.6
R-Calcarine	2	3	2	3	1	2	2	3	2	3	3	3	2	3	2	3	2	3	2	3	2.0	2.9
L-Calcarine	2	3	2	3	1	2	2	3	2	3	3	3	2	3	2	3	2	3	2	3	2.0	2.9
R-SCA	2	3	3	3	2	3	2	2	2	2	1	1	1	1	2	2	2	3	2	2	1.9	2.2
L-SCA	3	3	3	3	2	3	2	2	2	2	1	2	2	2	2	3	1	1	1	2	1.9	2.3
Total	19	25	22	28	17	26	20	24	17	22	19	22	19	23	18	24	17	24	17	24	18.5[b]	24.2[c,d]

CVD	Case 11		Case 12		Case 13		Case 14		Case 15		Case 16		Case 17		Case 18		Case 19		Case 20[e]		Mean	
	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
R-angular	1	1	2	2	2	3	1	2	1	2	1	2	2	3	1	2	1	2	1	1	1.3	2.0
L-angular	1	2	2	2	2	2	2	2	1	2	2	2	2	2	1	2	1	2	1	1	1.5	1.9
R-insular	1	2	1	1	1	2	1	2	1	2	2	2	2	3	1	1	1	2	2	2	1.3	1.9
L-insular	1	2	1	1	2	3	1	2	1	2	2	3	2	2	1	1	1	2	1	1	1.3	1.9
R-P.com	3	3	2	2	1	1	1	1	1	1	1	2	3	3	1	1	1	2	1	1	1.5	1.7
L-P.com	1	1	3	3	1	1	1	1	1	1	2	2	1	2	1	1	1	1	1	1	1.3	1.4
R-Calcarine	2	3	2	2	2	2	2	2	2	3	2	2	2	2	1	1	2	2	1	1	1.8	2.0
L-Calcarine	2	3	2	2	2	2	2	2	2	2	2	2	2	2	1	1	2	2	3	3	2.0	2.1
R-SCA	1	1	2	2	1	2	3	3	2	2	3	3	3	3	1	1	2	2	1	1	1.9	2.0
L-SCA	3	3	2	2	1	2	3	3	2	2	3	3	2	2	1	1	2	2	1	1	2.0	2.1
Total	16	21	19	19	15	20	17	20	14	19	20	23	21	24	10	12	14	19	13	13	15.9	19.0[f]

Note.—1 indicates not depicted; 2, fairly depicted; 3, well depicted; B, baseline; A, acetazolamide; R, right; L, left; P.com, posterior communicating artery; SCA, superior cerebellar artery; and CVD, cerebrovascular disease.

[a] See Figure 1.

[b] $P < .05$; significantly different from patients with CVD.

[c] $P < .01$; significantly different from patients with CVD.

[d] $P < .001$; significantly different from baseline.

[e] See Figure 2.

[f] $P < .01$; significantly different from baseline.

ranged in age from 34 to 76 years (mean, 50) and had no neurological symptoms. All subjects underwent standard spin-echo MR head imaging and all 10 patients also underwent digital subtraction angiography or conventional cerebral angiography.

In another 6 patients (all men), ranging in age from 50 to 67 years (mean, 60), each with a single stenotic lesion in their middle or posterior cerebral artery confirmed by digital subtraction angiography or conventional angiography, we investigated the usefulness of acetazolamide administration for the diagnosis of atherosclerotic stenosis in the main trunks of the major cerebral arteries.

MR Studies

MR studies were performed with a 1.5-T superconducting MR imaging system using a head coil and commercially available software.

Vascular MR imaging was performed with a 3-D time-of-flight technique. The imaging sequence used was spoiled gradient echo and its parameters included a repetition time of 34 msec, a system-selected echo time of 4.3 msec, two excitations, a 20° flip angle, a 128 × 256 matrix, an 18-cm field of view, and a 60-mm excitation volume divided into 60 1-mm-thick axial partitions. The frequency encoding direction was anteroposterior. Flow compensation and no phase wrap were used for all sequences.

A sagittal spoiled gradient-echo scout image was obtained to locate the target volume. 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 acetazolamide (Diamox, Lederle Japan, Tokyo, Japan) intravenously. Twenty minutes after acetazolamide injection, the second MR angiography was performed under the same conditions as the baseline MR angiography. Approximately 45 minutes was required for a series of examinations to be completed.

From each data set, collapsed axial angiographic images were created using a standard maximum intensity projection algorithm.

Interpretation of MR Imaging

The MR angiograms obtained before and after intravenous administration of acetazolamide were read by two

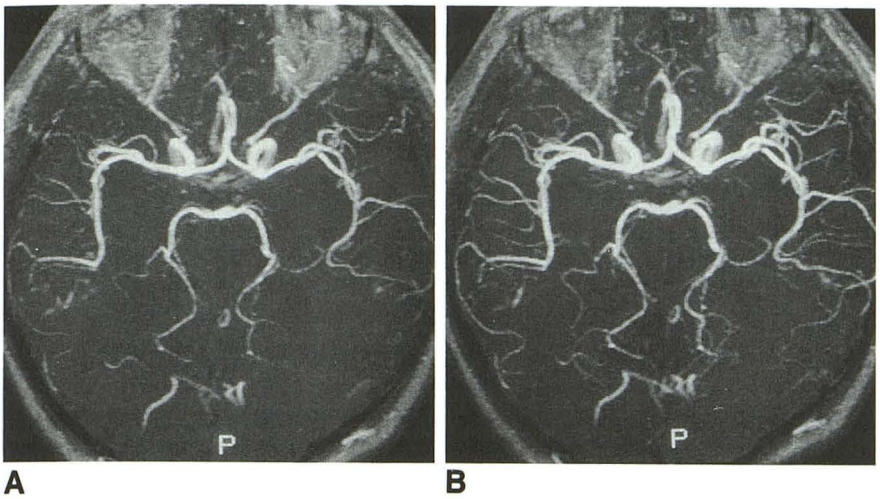

Fig. 1. Case 1, healthy subject. Axial collapsed 3-D time-of-flight imaging without (*A*) and with (*B*) acetazolamide. Visualization of small peripheral arteries is improved in *B*.

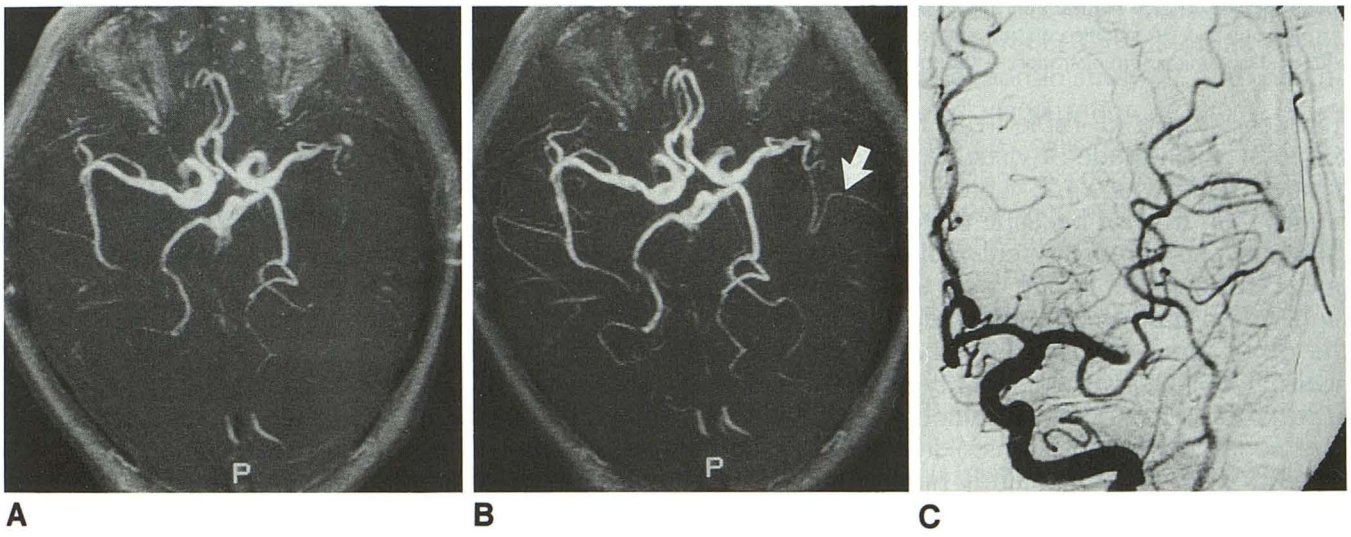

Fig. 2. Case 20. A case of huge cortical infarction in the left middle cerebral artery territory. Axial collapsed 3-D time-of-flight imaging without (*A*) and with (*B*) acetazolamide. Digital subtraction angiogram (*C*). The common trunk of his left middle cerebral artery is occluded after branching the patent posterior temporal artery in *C*. On the other hand, in MR angiograms, his left posterior temporal artery, which is not seen in *A*, is visualized in *B* (*arrow*).

readers (readers X and Y) without knowledge of acetazolamide administration or any patient's clinical data including the results of conventional angiography.

To evaluate the visualization of small arteries, these two readers independently graded the small arteries (insular branches, angular artery, posterior communicating artery, calcarine artery, superior cerebellar artery) as "not depicted," "fairly depicted," or "well depicted." Differences in grading between the readers were resolved by consensus after the images were reviewed at a separate session.

To evaluate the visualization of stenotic lesion in the main trunks of their major cerebral arteries, these two readers independently analyzed middle or posterior cerebral arteries of another group of 6 patients with a single stenotic lesion in their middle or posterior cerebral artery, as "normal," "stenotic," or "occluded."

Results

Imaging of Small Peripheral Intracranial Arteries

In most subjects, visualization of small arteries was improved with acetazolamide in varying degrees (Table 1). However, signals from the other intracranial structures were not augmented by acetazolamide. Several small peripheral arteries that had not been seen on the baseline MR angiogram were detected after acetazolamide administration. Two pairs of MR angiograms are shown in Figures 1 and 2.

The grades of visualization of insular branches, angular artery, posterior communicating artery, calcarine artery, and superior cerebellar artery are

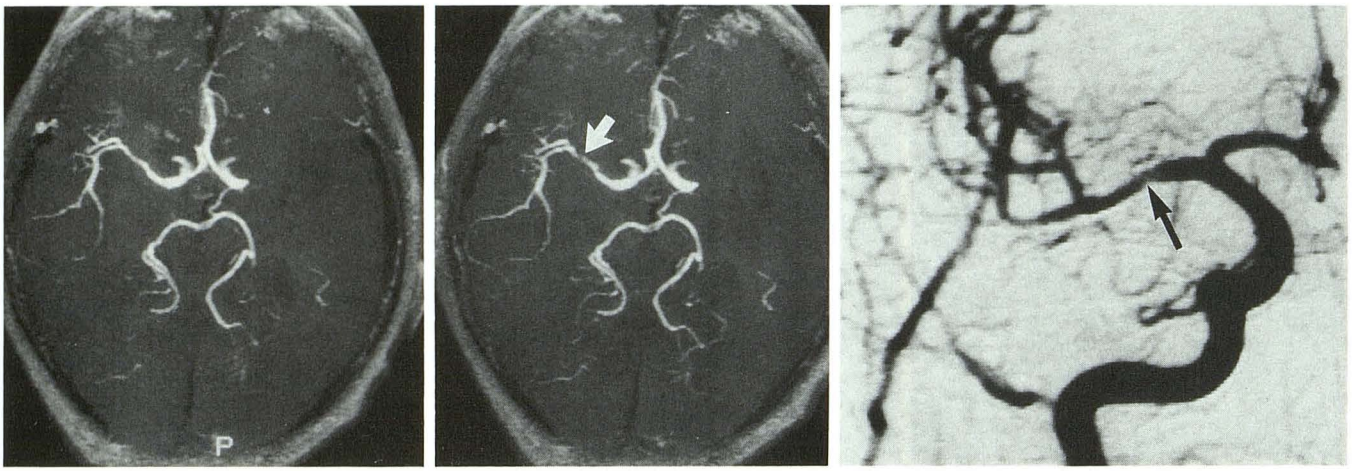

Fig. 3. Case 24. A case of multiple cortical infarctions. Axial collapsed 3-D time-of-flight imaging without (*A*) and with (*B*) acetazolamide. Digital subtraction angiogram (*C*). Digital subtraction angiography revealed mild right middle cerebral artery stenosis (*arrow* in *C*) and left middle cerebral artery occlusion. In MR angiograms, visualization of the peripheral arteries is not much improved with acetazolamide administration. Although it is slight, visualization of right middle cerebral artery stenosis is improved on *B* (*arrow*).

minutely shown in Table 1. In healthy subjects, the total mean grade of visualization on acetazolamide image was 24.2, which was significantly higher than that on baseline image ($P < .001$). In patients with cerebrovascular disease, the score on acetazolamide image was also significantly higher than that on baseline image ($P < .01$). On the other hand, the score on baseline image in healthy subjects was signiicantly higher than that in patients with cerebrovascular disease ($P < .05$). The score on acetazolamide image in healthy subjects was also significantly higher than that in patients with cerebrovascular disease ($P < .01$). When the improvement in visualization of small arteries with acetazolamide administration was defined as the difference between the total mean grade of visualization on acetazolamide image and that on baseline image, it was 3.1 in patients with cerebrovascular disease, which was lower than the 5.7 in healthy volunteers.

In brief, not only visualization of small arteries on both baseline and postacetazolamide images, but also its improvement with acetazolamide administration was better in healthy subjects than in patients with ischemic cerebrovascular disease.

Imaging of Stenosis

Stenotic lesions in the main trunks of the major cerebral arteries could be detected more clearly on acetazolamide images than on baseline images. Three pairs of MR images and conventional angiograms or digital subtraction angiograms are shown in Figures 3–5.

The diagnoses by two readers of the stenotic lesions in the 6 patients are shown in Table 2. On the baseline image, both readers correctly diagnosed the 22 arteries out of 24 arteries of the 6 patients; they made two wrong diagnoses. After the acetazolamide administration, all readings were correct. For each reader, the sensitivity for correct identification of major arteries with "stenosis" was 66% without acetazolamide administration; however, it was 100% with acetazolamide administration. The agreement between the two readers for diagnosis was 92% without acetazolamide administration, 100% with acetazolamide administration.

No one complained of serious adverse effects of acetazolamide administration. Someone complained of transient facial numbness and lightheadedness.

Discussion

MR angiography is a noninvasive procedure for evaluating the cerebral arteries, but it provides inadequate information about small peripheral vessels. Some methods have been designed previously to evaluate small vessels with 3-D time-of-flight MR angiography. Lewin and Laub (7) have reported that small vessel visualization was best obtained with a multiple thin-volume technique. Hendrix et al (8) stated that surface coil MR angiography could serve as a useful adjunct to routine head coil MR angiography in the evaluation of peripheral vascular abnormalities. Edelman et al (9) reported that use of magnetization

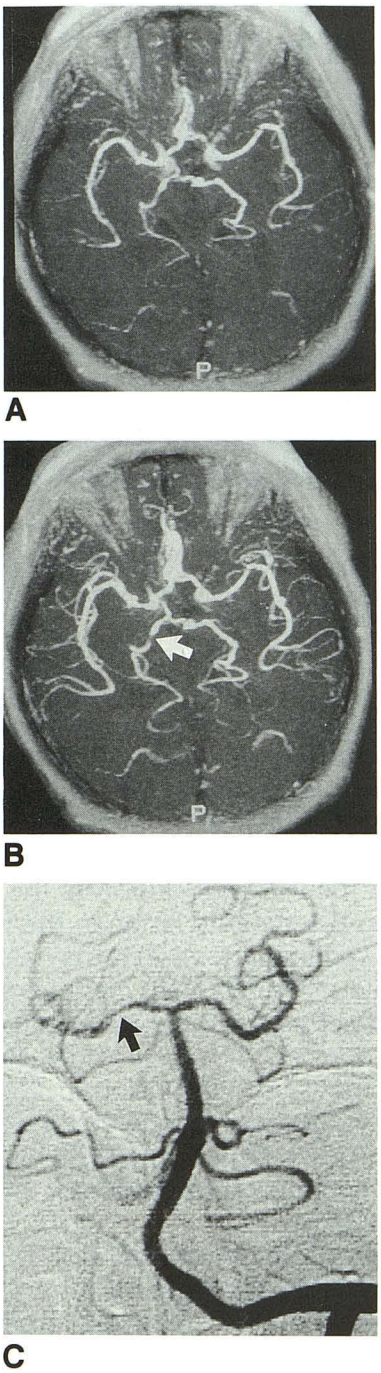

Fig. 4. Case 25. A case of lacunar infarction. Axial collapsed 3-D time-of-flight imaging without (*A*) and with (*B*) acetazolamide. Digital subtraction angiogram (*C*). The stenotic lesion (*arrow*) in the right posterior cerebral artery revealed by digital subtraction angiography is detected more clearly in *B* (*arrow*) than in *A*.

transfer contrast pulses in conjunction with 2-D and 3-D flow-compensated gradient-echo sequences results in substantial improvement in small vessel conspicuity in time-of-flight MR angiography. We aimed to evaluate small peripheral intracranial arteries without using any special equipment, so our study was done with commercially available standard MR apparatus and software.

To visualize arterial lesions by the 3-D time-of-flight technique, it is advantageous that signals from intracranial structures other than the arteries are not augmented by acetazolamide administration. Gadopentetate dimeglumine does increase signals from veins and other intracranial structures (10). So the diagnostic value of our method is enhancement of arterial vasculature without augmentation of noises from other components of the brain.

Acetazolamide, a cerebral vasodilatory stimulus, is known to increase cerebral blood flow immediately after intravenous injection. Several clinical studies using Doppler ultrasonography (5,11) and cerebral blood flow studies (2,6,12–15) have shown that cerebral blood flow increases after acetazolamide administration. We postulated that improved visualization of small intracranial arteries and stenosis might be achieved by the rapid increment of cerebral blood flow induced by the vasodilation after acetazolamide administration. Augmented blood flow increases the proportion of unsaturated spins in a section, consequently the signal intensity of the peripheral arteries may be increased. Visualization of stenosis also may be improved if flow at the stenosis becomes more turbulent, so that the flow void effect at the stenosis becomes stronger, and if visualization of the distal artery is improved. We confirmed that the signal intensities with spoiled gradient-echo sequence of the physiological saline and of the Diamox solution in physiological saline were the same, indicating that the improvement of visualization with acetazolamide administration is not artificial.

The improvement of visualization of small peripheral arteries tended to be better in the healthy subjects than in the patients with ischemic cerebrovascular disease. This phenomenon might be consistent with the results obtained from single-photon emission computed tomography studies (15) showing that the vascular reactivity to acetazolamide is diminished in patients with cerebrovascular disease. In the patients with severe generalized atherosclerosis, acetazolamide slightly improved visualization of the small artery in our study. The effect of acetazolamide, which diminishes in those vessels, might suggest the severity of atherosclerosis. This fact indicates that cerebral vasoreactivity could be estimated quantita-

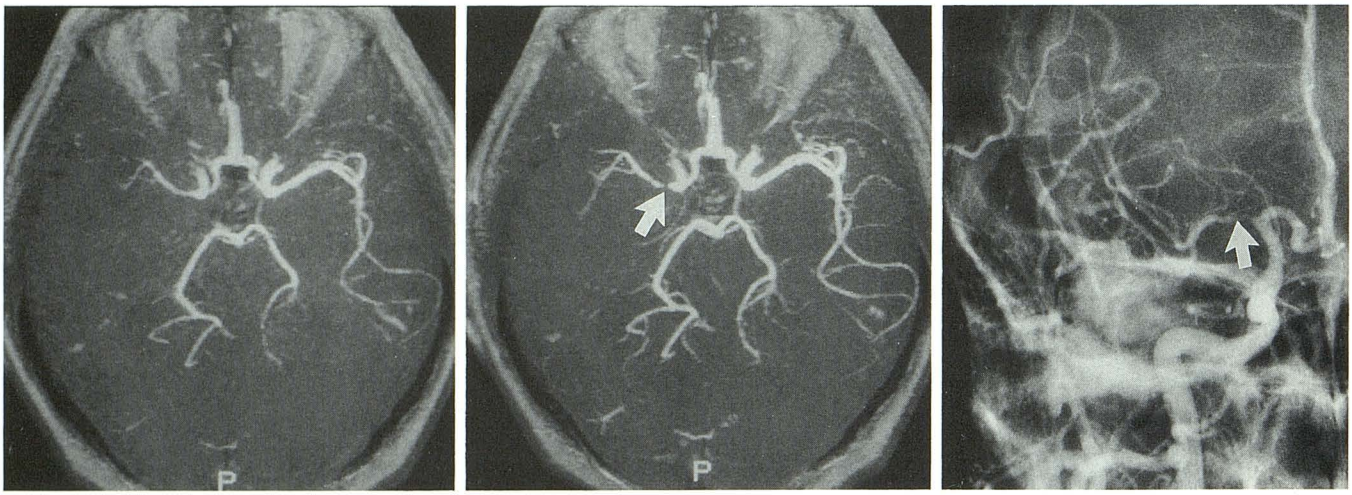

Fig. 5. Case 26. A case of cortical infarction in right middle cerebral artery territory. Axial collapsed 3-D time-of-flight imaging without (*A*) and with (*B*) acetazolamide. Conventional angiogram (*C*). The stenotic lesion (*arrow*) at the root of the right middle cerebral artery revealed by conventional angiography is difficult to see in *A*, but is clearly detected in *B* (*arrow*).

TABLE 2: Diagnosis of stenotic lesion

Case	Artery with Stenosis	Reader	MR Diagnosis[a]	
			Baseline	Acetazolamide
21	R MCA	X	2	2
		Y	2	2
22	L MCA	X	2	2
		Y	2	2
23	L MCA	X	2	2
		Y	2	2
24[b]	R MCA	X	2	2
		Y	1	2
25[c]	R PCA	X	1	2
		Y	2	2
26[d]	R MCA	X	3	2
		Y	3	2

Note.—R indicates right; L, left; MCA, middle cerebral artery; and PCA, posterior cerebral artery.

[a] 1 normal; 2, stenotic; 3, occluded.

[b] See Figure 3.

[c] See Figure 4.

[d] See Figure 5.

tively with acetazolamide administration and 3-D time-of-flight MR angiography.

MR angiography has been shown to be useful in screening for extracranial atherosclerotic lesions at the carotid bifurcation (1). However, in detecting intracranial atherosclerotic lesions, especially peripheral lesions, MR angiography is inferior to conventional cerebral angiography. In our study, the visualization of the small peripheral arteries was improved and the stenotic lesions in the main trunks of their major cerebral arteries were detected more clearly after acetazolamide administration by 3-D time-of-flight MR angiography. Moreover, in the diagnosis of occlusion in major cerebral artery, the false-positive diagnoses may be decreased with acetazolamide administration as in Figures 2 and 5 and Table 2.

The clinical significance of acetazolamide administration with 3-D time-of-flight MR angiography is as follows: 1) It improves the sensitivity in detecting the stenotic lesion in the main trunk of a major cerebral artery. 2) It may also improve the sensitivity of detecting peripheral vascular abnormalities by improving visualization of small peripheral arteries. 3) It may decrease the false-positive diagnoses of occlusion in the major arteries. 4) It could lead to functional diagnosis by estimating the cerebral vasoreactivity with acetazolamide administration and 3-D time-of-flight MR angiography.

We conclude that acetazolamide improves the visualization of small peripheral intracranial arteries and sensitivity in detecting atherosclerotic stenosis in the main trunk of major cerebral artery by 3-D time-of-flight MR angiography without the necessity of a change in MR apparatus or software.

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