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Susceptibility-Weighted MR for Evaluation of Vasodilatory Capacity with Acetazolamide Challenge

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PURPOSE: To investigate cerebral vasodilatory capacity by acetazolamide challenge in healthy subjects and in patients with chronic occlusive cerebrovascular disease by using susceptibility-weighted gradient-echo MR imaging. **METHODS:** Eight patients with chronic occlusive cerebrovascular disease and four healthy volunteers were studied with susceptibility-weighted MR imaging before and after intravenous administration of 1000 mg of acetazolamide. Signal intensities were measured as a function of time in several regions of interest defined on anatomic images. In all patients with chronic occlusive cerebrovascular disease, acetazolamide challenge and resting regional cerebral blood flow were also evaluated with single-photon emission CT (SPECT). **RESULTS:** In healthy volunteers, signal intensities began to increase at 3 to 4 minutes after acetazolamide administration, with a continuous increase during the subsequent 10 minutes. The effect lasted for approximately 45 minutes after administration. In patients with chronic occlusive cerebrovascular disease, signal changes on susceptibility-weighted MR images of occluded areas with normal vasodilatory capacity on SPECT images did not differ from signal changes of nonocclusive areas. In those patients with changes that reflected diminished vasodilatory capacity, the MR images showed a lower percentage of signal changes after acetazolamide administration than those in normally perfused areas. **CONCLUSION:** Susceptibility-weighted MR imaging offers an alternative method for estimating vasodilatory capacity.

Index terms: Blood, magnetic resonance; Cerebral blood flow; Magnetic resonance, gradient-echo

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Recently, new techniques have been developed for studying human brain function by using magnetic resonance (MR) imaging technology. One of these techniques exploits differences in the magnetic susceptibility of oxygenated and deoxygenated hemoglobin to track blood flow-related phenomena with high temporal and spatial resolution (1). This MR technique, called the *blood oxygen level dependent* (BOLD) contrast method, has been used to show visual, motor, and sensory activation

maps with echo-planar imaging (1-5). The BOLD effect also has been observed in conventional MR imaging systems operating at 1.5 T with long-echo-time susceptibility-weighted gradient-echo pulse sequences (6-8). Acetazolamide has been proved to increase cerebral blood flow in studies using xenon-133 single-photon emission computed tomography (SPECT) and positron emission tomography, but it has no effect on oxidative metabolism (9, 10). We postulate that susceptibility-weighted gradient-echo MR imaging can show an increase of cerebral blood flow caused by the acetazolamide challenge as an increased signal intensity caused by the BOLD effect. The aim of this study was to investigate whether cerebral vasodilatory capacity can be shown by the acetazolamide challenge in healthy subjects and in patients with chronic occlusive cerebrovascular disease by using susceptibility-weighted gradient-echo MR imaging.

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Subjects and Methods

Subjects

We studied four healthy volunteers (four men; mean age, 32 years; age range, 28 to 35 years) and eight patients (four men, four women; mean age, 68 years; age range, 56 to 82 years) with unilateral chronic occlusive cerebrovascular disease (nine territories). In the volunteers, extracranial and intracranial arteries were confirmed to be normal by three-dimensional time-of-flight (TOF) angiography and 3-D phase contrast angiography. All patients with chronic occlusive cerebrovascular disease had had either minor strokes or transient ischemic attacks. Transarterial catheter cerebral angiography, brain MR imaging, and MR angiography were performed in all patients before the regional cerebral blood flow (rCBF) studies that used SPECT and susceptibility-weighted MR imaging. All procedures were approved by the ethics committee at the Junwakai Memorial Hospital. The volunteers and patients were informed both orally and in writing about the MR study and drug application (intravenous bolus injection of 1000 mg acetazolamide).

MR Imaging Protocol

MR imaging studies were done on a 1.5-T superconductive MR system with a standard head coil but without any special head-restraint mechanism to eliminate patient motion. Before the MR study, patients and volunteers were informed that BOLD imaging was very sensitive to head movement. Anatomic imaging was done by using fast spin-echo T1-weighted (450/20/3 [repetition time/echo time/excitations]) and T2-weighted (3000/100/2) MR sequences. Three-dimensional TOF angiography and 3-D phase-contrast angiography were performed by using a spoiled gradient-recalled acquisition in the steady state sequence with the following parameters: TOF, 40/7 (repetition time/echo time); phase-contrast, 23/9; TOF, 25° flip angle; phase-contrast, 20° flip angle. BOLD images were obtained by using a spoiled gradient-recalled acquisition in the steady state sequence: 90/44/2; flip angle, 30°; field of view, 22 cm; section thickness, 7 mm (single section); and matrix, 128 × 128. The section level of the susceptibility-sensitive MR study included the upper margin of the lateral ventricle for all volunteers and the same level or the level including basal ganglia for patients with cerebrovascular disease. The protocol consisted of dynamic susceptibility-weighted MR imaging with 37-second intervals.

Acetazolamide (1000 mg) was administered intravenously after 4 minutes. The measuring times of the dynamic susceptibility-weighted MR sequences were 28 minutes for patients with chronic occlusive cerebrovascular disease and 49 minutes for healthy volunteers. Four images were obtained before acetazolamide administration and were averaged as rest images. Difference maps were calculated by subtracting the averaged images at rest from those acquired 20 minutes after acetazolamide adminis-

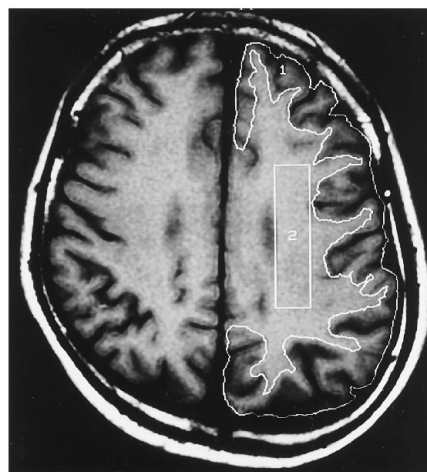


Fig 1. Setting for the regions of interest on cortex and white matter on MR images of healthy volunteers.

tration. Signal intensities were measured as a function of time in several regions of interest defined on anatomic images. In healthy volunteers, the regions of interest were placed on the cortical area and white matter (Fig 1). In patients, the regions of interest were placed on stenotic vascular territories (middle cerebral artery territory for patients with lesions of the middle cerebral artery and internal carotid artery, and posterior cerebral artery territory for patients with lesions of the posterior cerebral artery) and on contralateral nonstenotic vascular territories.

SPECT Imaging Protocol

In all patients with chronic occlusive cerebrovascular disease, acetazolamide challenge and resting rCBF SPECT studies were performed before susceptibility-sensitive MR studies. SPECT scans were obtained by using a dual-head gamma camera system with high-resolution collimators (full width at half-maximum intensity, 11 mm). SPECT was performed in 64 steps, 360°, and with a 128 × 128 matrix. The SPECT studies were carried out with a split-dose technique. The first dose of 370 MBq of technetium-99m ethyl cysteinate dimer (^{99m}Tc-ECD) was injected when the subject was in the resting state. Fifteen minutes after the ^{99m}Tc-ECD had been injected, 1000 mg of acetazolamide was injected while the first SPECT study (rest image) with 15 seconds per step was started. Immediately after the first SPECT study, without any repositioning of the patient, an additional 740 MBq of ^{99m}Tc-ECD was injected. Fifteen minutes after the second injection of ^{99m}Tc-ECD, a second SPECT study was started, with 15 seconds per step. Acetazolamide-challenge images were calculated by subtracting the first SPECT images from the second SPECT images. The limitation of the vasodilatory capacity in the affected area was estimated by the asymmetry index difference between the rest image and the acetazolamide-challenge image. The asymmetry index was calculated as $100 \times C_a/C_u$, where C_a is the mean

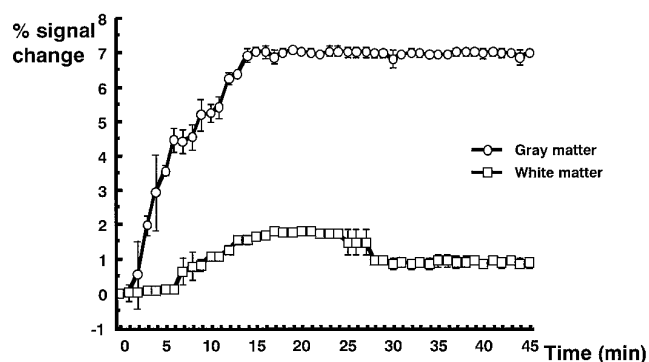


Fig 2. Percentage of signal changes over time after acetazolamide administration for regions in cortical gray matter and deep white matter in healthy volunteers. Error bar, ± 1 SD.

reconstructed counts for the affected area and C_u is the mean reconstructed counts for the contralateral unaffected area. The asymmetry index difference was calculated as the asymmetry index of the rest image subtracted from the asymmetry index of the acetazolamide-challenge image. Affected areas were classified into two groups according to acetazolamide reactivity on SPECT; the positive group (reduced vasodilatory capacity) had an asymmetry index difference of less than -10% , and the negative group had an asymmetry index difference of -10% or higher.

Statistical Analyses

Statistical analyses were carried out by ANOVA (repeated measurements for response to acetazolamide). Multiple comparisons with a group of healthy subjects were made with Dunnett's test. In Dunnett's test, a significant difference is present when $P < .05$. The correlation between the asymmetry index on the SPECT image and the percentage of signal change on the MR image was analyzed by means of a simple linear regression model. These analyses were carried out using the JMP Macintosh program (SAS Institute Inc, Cary, NC).

Results

Healthy Volunteers

Figure 2 shows the time courses of signal change in the cortical gray matter and the white matter in healthy volunteers after acetazolamide administration. In the cortical gray matter, signal intensities began to increase 3 to 4 minutes after acetazolamide administration ($1.98\% \pm 0.29$), with a continuous increase during the subsequent 10 minutes ($6.93\% \pm 0.21$); the effect lasted during the whole examination period. In the white matter, lesser but still significant increases in signal intensities were observed from 7 minutes after acetazolamide ad-

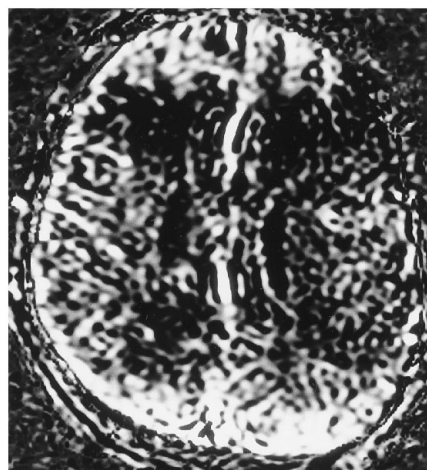


Fig 3. Difference map obtained by subtracting averaged rest images from an image obtained 20 minutes after administration of acetazolamide in a healthy volunteer. Difference map shows increased signal intensity mainly in the brain cortex and a smaller signal increase in the white matter.

ministration ($0.65\% \pm 0.38$), with continuous increases during the subsequent 10 minutes ($1.81\% \pm 0.05$). Mild declines in signal occurred from 24 to 30 minutes after acetazolamide administration ($0.96\% \pm 0.06$). The signal changes caused by acetazolamide administration were more pronounced in cortical gray matter but were also observed in white matter. The signal increase can be shown by subtracting an averaged rest image from an image acquired 20 minutes after acetazolamide administration (Fig 3).

Patients with Chronic Occlusive Cerebrovascular Disease

Cerebral angiography showed unilateral atherosclerotic vascular lesions in the trunk of the middle cerebral artery in three patients (two with occlusion and one with severe stenosis), in the internal carotid artery in five patients (one with occlusion, two with moderate stenoses, and two with mild stenoses), and in the posterior cerebral artery occlusion in one patient. (The North American Symptomatic Carotid Endarterectomy Trial method was used for quantifying vascular stenosis.) Lacunar infarctions in the basal ganglia and white matter in the middle cerebral artery territory were observed in all patients, and MR imaging showed a small cortical infarction in the middle cerebral artery-posterior cerebral artery border zone in one patient. Of nine ischemic vascular territories seen

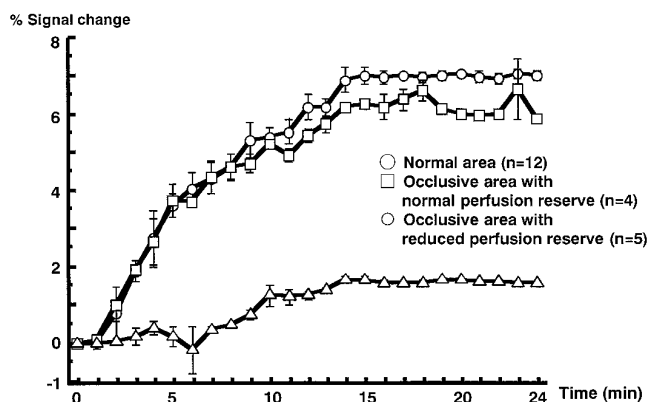


Fig 4. Percentage of signal changes over time on each cortical area after acetazolamide administration in healthy volunteers and in patients with chronic occlusive cerebrovascular disease.

on SPECT scans, five had reduced vasodilatory capacity (four occlusions and one severe stenosis), and four had normal vasodilatory capacity (two mild stenoses and two moderate stenoses). In internal carotid artery lesions, reduced vasodilatory capacity was observed in the middle cerebral artery territory. Figure 4 shows the time courses of signal change after acetazolamide administration in each cortical area in healthy volunteers and in patients with chronic occlusive cerebrovascular disease. The percentage of signal change of occlusive areas that showed normal vasodilatory response with the acetazolamide test did not differ from that of normal areas. However, the percentage of signal change from 3 to 25 minutes after acetazolamide administration in occlusive areas that showed reduced vasodilatory response with acetazolamide test were significantly lower than those of both normal areas and occlusive areas with normal vasodilatory response ($P < .05$, Dunnett's test). A small decrease in signal intensity ($-0.19\% \pm 0.62$) was observed 6 minutes after acetazolamide administration in patients with reduced vasodilatory capacity. Figure 5 shows the correlation between the asymmetry index difference on SPECT and the averaged percentage of signal change on susceptibility-weighted MR images from 14 minutes to 24 minutes after acetazolamide administration for patients with chronic occlusive cerebrovascular disease. The correlation coefficient was $r = .96$ ($P < .01$), and the slope of the computed regression line was 0.24. Figure 6 shows the cerebral angiogram, the T2-weighted MR image, SPECT images, and the difference map of susceptibility-weighted MR images in a

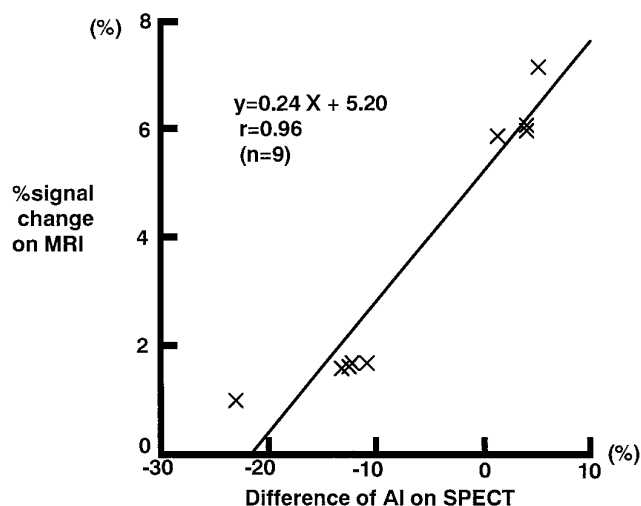


Fig 5. The correlation between the asymmetry index (*AI*) differences (ie, asymmetry indexes of acetazolamide-activated images minus those of rest images) on SPECT and the averaged percentage of signal change on the susceptibility-weighted MR image (*MRl*) from 14 to 24 minutes after acetazolamide administration in eight patients with chronic occlusive cerebrovascular disease (one patient had two atherosclerotic territories).

patient with a right middle cerebral artery occlusion and decreased perfusion reserve. SPECT images show reduced blood flow in the area of the right middle cerebral artery in the resting state and enhanced asymmetry in the area of the right middle cerebral artery in the acetazolamide-activated state. The difference map of susceptibility-weighted MR images shows smaller signal increase in the area of the right middle cerebral artery, and this map is similar to the acetazolamide-activated SPECT image.

Discussion

Acetazolamide is a potent cerebral vasodilator and has been used to estimate the hemodynamic reserves of the brain with rCBF SPECT, positron emission tomography, and stable-xenon CT (9–14). Acetazolamide blocks the conversion of carbonic acid to CO_2 and H_2O inside the brain (15, 16). After the administration of acetazolamide, a gradual decline of pH in the brain tissue has been observed despite the maintenance of a constant brain tissue PaCO_2 . The decrease in pH is probably explained by cerebral carbonic acidosis, an increase in H_2CO_3 , and the dissociation products H^+ and HCO_3^- . Although acetazolamide induces a rapid and significant increase in CBF, this in-

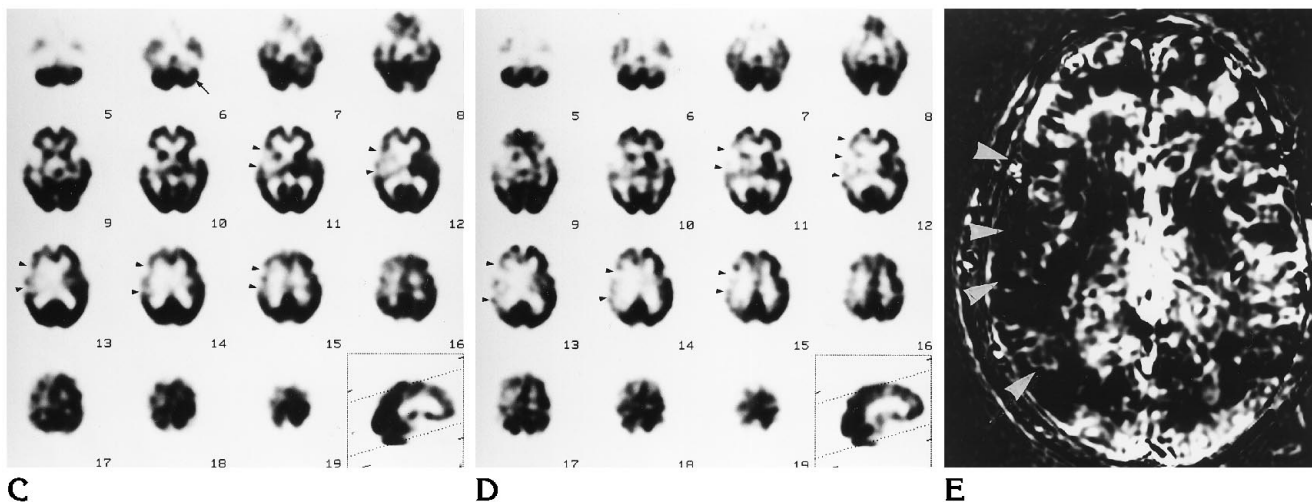
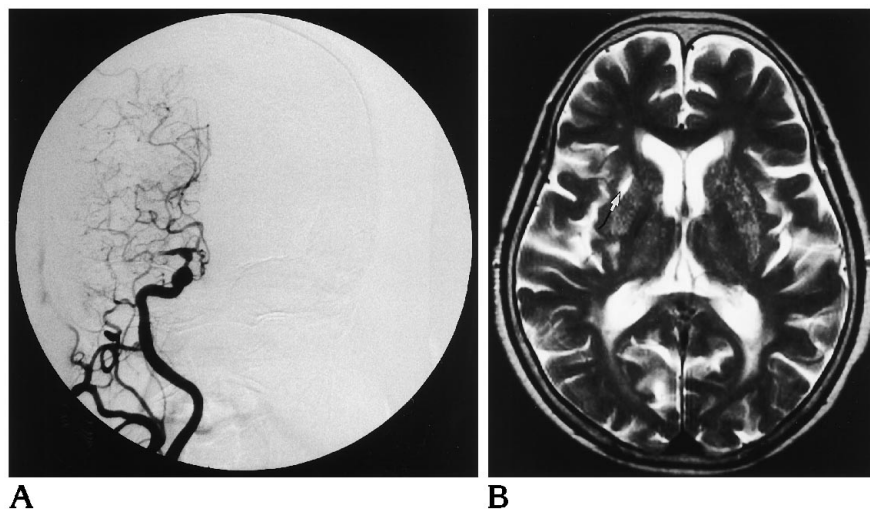


Fig 6. Woman 82 years old with left hemiparesis diagnosed as minor stroke.

A, Right common carotid angiogram reveals an occlusion of the right middle cerebral artery (MCA).

B, T2-weighted MR image shows right putamen infarcts (arrow) without cortical infarction.

C, The resting SPECT images reveal an area of hypoperfusion in the right MCA territory (arrowheads) and crossed cerebellar diaschisis (arrow).

D, Acetazolamide-activated SPECT images reveal a limitation of vasodilatory capacity in the right MCA territory (arrowheads).

E, Difference map obtained by subtracting averaged rest images from images obtained 20 minutes after administration of acetazolamide. Difference map shows smaller increased signal intensity in the right MCA territory (arrowheads) than in other areas.

crease is not in parallel with function and oxidative metabolism (9–11). This physiological uncoupling causes a rise of cerebral blood oxygenation and a relatively decreased level of blood deoxyhemoglobin, which is detectable as an increase in signal intensity on susceptibility-weighted MR images. A similar uncoupling of CBF and oxidative metabolism occurs during the functional activation used for functional MR imaging using the BOLD technique (1–8). In our study of healthy volunteers, signal intensities began to increase from 3 to 4 minutes after acetazolamide administration, with a continu-

ous increase during the subsequent 10 minutes. The effect lasted at least 45 minutes after administration. This time course of signal intensities on MR images is similar to CBF changes seen on xenon-133 SPECT scans after acetazolamide administration (9). Vorstrup et al (9) reported that an increase in CBF occurred after 3 minutes, with a further increase at 20 minutes after acetazolamide administration, but the cerebral metabolic rate for oxygen remained stable. These facts indicate that an increase in signal intensity after the acetazolamide challenge on susceptibility-weighted MR images

probably reflects an increase in CBF and a constant oxidative metabolism. On the other hand, in our study of patients with chronic occlusive cerebrovascular disease, signal changes on MR images in the group that showed good perfusion reserve on SPECT scans did not differ from those of normal areas, whereas signal changes in the group with diminished reserve by SPECT were significantly lower in occluded areas than in normal areas. The percentage of signal changes on MR images correlated well with the asymmetry index differences on SPECT scans. These results suggest that acetazolamide-challenge susceptibility-weighted MR imaging can help estimate vasodilatory capacity as can acetazolamide-challenge rCBF SPECT studies.

Contrast in gradient-echo MR images is affected by the flow into the observed plane, especially when both a large flip angle and a thin section are used. This may be a potential pitfall, because increased signal intensity may be caused not only by BOLD effects but also by inflow effects. Recently, Duyn et al (17) reported that large signal changes, seen on gradient-echo MR studies at 1.5 to 2 T, were dominated by direct inflow effects. We think that inflow effects also may have played an important role in our acetazolamide-challenge MR study. However, all the effects seen cannot be explained by inflow effects. Images from our volunteers show a small increase in signal intensity in deep white matter during acetazolamide challenge. We postulate that the signal changes in white matter are mainly caused by BOLD effects. In addition, signal changes in brain cortex seen on the susceptibility-weighted MR images are smaller than would be expected if they were caused only by inflow effects resulting from changes in flow velocity.

The response of cerebral perfusion to vasodilatory stress is of clinical interest in patients with suspected hemodynamically relevant atherosclerotic disease. The effect of chronic occlusive cerebrovascular disease on cerebral perfusion depends on the potential collateral circulation and on the ability of the cerebral arteries to dilate when perfusion pressure decreases. Recent studies have shown that an occluded or stenotic carotid artery carried an increased risk of ischemic episodes in the hemisphere if the vasodilatory capacity of the distribution territory of the artery was lower than normal (9, 11, 12). Extracranial-intracranial bypass surgery has been shown to improve the

cerebrovascular reserve capacity in such patients (9, 11). Positron emission tomography is the reference standard for assessing cerebral perfusion because of its potential to quantify CBF, cerebral blood volume, and fractional oxygen extraction. However, the greater expense and technical complexity excludes positron emission tomography for routine clinical use. The SPECT technique, with tracers for CBF measurements such as iodine-123 *N*-isopropyl-p-iodoamphetamine, technetium-99m hexamethyl-propyleneamine oxime, and ^{99m}Tc ECD have been widely used for assessing cerebral perfusion. The usefulness of the rCBF SPECT study with acetazolamide challenge or carbon dioxide inhalation has already been reported in patients with occlusive cerebrovascular disease (12, 13). However, we think that the SPECT technique with the acetazolamide challenge but without quantitative determination of rCBF has two problems. First, evaluating the vasodilatory capacity by using the asymmetry index is difficult in patients with bilateral occlusive lesions, because the asymmetry index is useful only when the unaffected side is normal. Second, after the administration of a vasoactive drug, detecting the "intracerebral steal phenomenon" (11), which is a paradoxical decrease in CBF within hemodynamically compromised tissues, is difficult (12). In our study, susceptibility-weighted MR images showed a small decreased signal intensity in occlusive areas with decreased vasodilatory response 6 minutes after acetazolamide administration. We suspect that this decreased signal intensity may reflect CBF that is decreased because of intracerebral steal. This study shows that susceptibility-weighted MR imaging may become a useful technique for estimating vasodilatory capacity. We think that susceptibility-weighted MR imaging is attractive for several reasons: widespread availability, lack of ionizing radiation, and its high spatial and temporal resolution. It has possibilities for detecting intracerebral steal as a decrease in signal intensity and for evaluating bilateral occlusive lesions.

In conclusion, we found that susceptibility-weighted MR images could detect rCBF change caused by acetazolamide administration. This technique may prove useful in evaluating cerebral perfusion reserve in patients with chronic occlusive cerebrovascular disease.

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