Detection of Deoxygenation-Related Signal Change in Acute Ischemic Stroke Patients by T2*-Weighted Magnetic Resonance Imaging

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Background and Purpose—Acute decreases in the MR T2*-weighted signal have been reported in experimental models of middle cerebral artery occlusion. This has been attributed to blood deoxygenation in association with an increased brain oxygen extraction fraction. The aim of this study was to detect this signal by susceptibility-weighted MR imaging in acute ischemic stroke patients.

Methods—Dynamic susceptibility contrast-enhanced MR (DSC-MR) imaging was performed within 4 hours of stroke onset in 6 patients with unilateral cerebral artery occlusion (middle cerebral artery, n=5; internal carotid artery, n=1). Cerebral blood volume was estimated on a pixel-by-pixel basis. DSC-MR images taken before arrival of the contrast medium were examined visually to identify hypointense areas. Bilateral regions of interest were set in the middle cerebral artery territory for comparison of the mean signal intensity. A semilogarithmic plot of signal intensity versus cerebral blood volume for every pixel in the region of interest was also analyzed.

Results—The side on which the hypointense area was seen was significantly correlated with the side of arterial occlusion. The mean signal intensity was significantly smaller on the affected side than on the contralateral side. The semilogarithmic plot of signal intensity versus cerebral blood volume indicated greater deoxyhemoglobin concentrations for the ipsilateral than for the contralateral region of interest.

Conclusions—DSC-MR images allow detection of hypointensity in the affected cerebral hemisphere in acute ischemic stroke patients. Such hypointensity may indicate increased oxygen extraction fraction (misery perfusion) and may provide information valuable to patient care. (Stroke. 2002;33:967-971.)

Key Words: cerebral infarction ■ hemoglobin ■ magnetic resonance imaging, perfusion weighted ■ oxygen

Misery perfusion is a condition of an increased brain oxygen extraction fraction (OEF) observed by PET in brain regions with reduced cerebral blood flow (CBF) but relatively preserved oxygen metabolism.1 It is an indicator of tissue at risk for infarction but potentially salvageable (eg, penumbra) in the ischemic brain.2 In cat models of middle cerebral artery (MCA) occlusion, a persistent increase in OEF during ischemia was shown to indicate viability of tissue after restoration of CBF.3 In studies of early stroke patients, misery perfusion with slightly impaired oxygen metabolism did not result in infarction.4,5 In contrast, decreased OEF in the ischemic brain resulted in irreversible tissue damage with remarkably low oxygen metabolism.6–8

MR imaging is a potential alternative method for detecting misery perfusion. Increased OEF should lead to increased blood deoxyhemoglobin concentrations in cerebral capillaries and veins. Because deoxyhemoglobin is paramagnetic and oxyhemoglobin is diamagnetic, changes in hemoglobin oxygenation levels affect magnetic resonance signal intensities, which are blood oxygenation level dependent.9 Relaxation times T2 and T2* decrease as deoxyhemoglobin concentrations increase, which causes MR signal reduction. T2- and T2*-sensitive MR imaging has shown a rapid reduction in signal intensity after MCA occlusion in animals.10–13 The absolute T2 value also decreased in similar models.14 The change in the T2 value induced by experimental ischemia was significantly correlated with the magnitude of the blood oxygenation level–dependent effect.15 Signal reduction in T2- and T2*-sensitive MR imaging studies, however, has not been reported in acute stroke patients.

With the increasing availability of echo-planar imaging in recent years,16 dynamic susceptibility contrast-enhanced MR (DSC-MR) imaging17,18 has become a familiar clinical means of evaluating disturbances in cerebral circulation. T2*-weighted gradient-echo echo-planar imaging in DSC-MR imaging is highly T2* sensitive. In DSC-MR images obtained before the first arrival of contrast medium to the brain, signal intensity may decrease locally in brain regions with increas-
ing deoxyhemoglobin concentrations. We tested our hypothesis that T2*-sensitive MR imaging can detect blood deoxygenation in the vascular territory of the occluded cerebral artery in patients with acute ischemic stroke.

Subjects and Methods

Patients

Six patients with acute ischemic stroke were studied retrospectively. The time of onset had been recorded for all 6 patients. All patients underwent CT and then DSC-MR imaging within 4 hours of symptom onset. MR angiography was performed in 5 patients, and conventional angiography was also performed in 5 patients. All 6 patients were covered by at least 1 of these angiography examinations. Five patients showed occlusion of the horizontal segment of the MCA, and 1 showed internal carotid artery (ICA) occlusion on the side consistent with symptoms. Follow-up angiography revealed recanalization in 5 of the patients. The remaining patient, who did not undergo follow-up angiography, showed recovery of CBF in the affected region on follow-up SPECT study. Informed consent was obtained from all patients or their relatives before the study, and the study was approved by our institutional review committee. Patient data are shown in the Table.

MR Imaging Studies

MR imaging was performed with a 1.5-T Siemens Vision system (Siemens Medical Systems) and a standard head coil. Axial fast spin-echo T2-weighted MR images [repetition time (TR), 3600 ms; echo time (TE), 96 ms; excitations, 1; slice thickness, 5 mm; slice gap, 1 mm; matrix size, 224×512; field of view, 230 mm] and 3-dimensional time-of-flight MR angiographic images (TR, 39 ms; TE, 6.5 ms; excitations, 1; slab thickness, 60 mm; partitions, 60; matrix size, 160×512; field of view, 200 mm) were acquired in 5 of the patients.

DSC-MR imaging studies were performed with axial single-shot gradient-echo planar imaging (TE, 54 ms; slice thickness, 5 mm; matrix size, 128×128; field of view, 230 mm; flip angle, 90°). Immediately after a bolus injection of 0.1 mmol/kg gadolinium-chelate (Gd-DTPA) into the antecubital vein, scanning was initiated. Sixty images per slice were obtained with a 1-second TR for 60 seconds in 5 slices, 1 at the level passing through the cerebellum and the other 4 in the cerebrum obtained 0, 12, 24, and 36 mm above and parallel to the anterior commissure–posterior commissure line.

After the DSC-MR scanning, T1-weighted spin-echo images (TR, 665 ms; TE, 14 ms; excitations, 2) were obtained in 5 patients to detect leakage of the contrast medium into brain parenchyma. None of the patients showed parenchymal enhancement.

Data Analysis

Images were transferred to a UNIX workstation (Sun Ultrasparc 20) to create maps of relative cerebral blood (plasma) volume (CBVp). Signal intensity variations during bolus passage of the contrast agent were converted to a concentration-time curve fitted to a gamma variate function on a pixel-by-pixel basis, as previously described.18,19 On the basis of tracer kinetics, relative CBVp was defined as the area under the concentration-time curve and calculated with MR Vision software (MR Co). Further analysis was performed for the 2 uppermost slices because image degradation resulting from the susceptibility effect of air in the paranasal sinuses and temporal bones was noted in the lower slices.

A precontrast image was created by averaging images before arrival of the contrast medium. The first and second images were excluded from the averaging, however, because they showed different signal intensities owing to the transient magnetization. A hypointense area in the MCA territory was defined as a region of apparent decreased signal intensity on the precontrast image compared with that of the contralateral mirror region. Twelve precontrast images for 6 patients were inspected visually and independently by 2 experienced neuroradiologists who were blinded to the clinical data; they were asked to identify on which side (hemisphere) the hypointense area existed. We evaluated whether the hypointense area ultimately became infarcted by studying follow-up MR images in 5 patients and CT images in 1 patient obtained ≥3 days later. Volumes of the hypointense areas were outlined manually and measured for the 2 uppermost slices. Results of 2 independent observers were averaged. Corresponding volumes of final infarcts were similarly determined.

The longitudinal relaxation time, T1, was also estimated on a pixel-by-pixel basis. The signal intensity of the precontrast image depends on T1 because of the acquisitions of 1-second repetition, whereas the signal of the first image is not affected by T1. On the basis of this signal behavior, we calculated a map of T1, similar to that described elsewhere.20 In short, a shift of the flip angle of the radio frequency pulse from 90° was estimated and incorporated into a formula that expresses the signal intensity as a function of T1. The T1 map was used as a filter to segment the images. Cerebral tissue was considered to have T1 <1100 ms21 and >250 ms.

An oval region of interest (ROI) was outlined on the segmented precontrast image and on the corresponding CBVp and T1 maps in the affected MCA territory. Another ROI was placed in the mirror region in the contralateral hemisphere. The placement of ROIs is shown in Figure 1. The following numerical analysis was restricted to pixels of the segmented cerebral region in each ROI.

The signal intensity of the precontrast image, SIpre, depends on T2* as well as T1:

\[
SI_{\text{pre}} = A \times e^{-\frac{T_1}{T_1^*}} \]

where A is a constant, and T1 is the time constant of the relaxation process. The signal intensity of the postcontrast image, SIpost, depends on T1 and T2* as well as T1:

\[
SI_{\text{post}} = A \times e^{-\frac{T_1}{T_1^*}} \times e^{-\frac{T_2^*}{T_2^*}}
\]
The association between the side of hypointensity described by radiologists and the side of the occluded artery was tested by Fisher’s exact probability test. The difference between the mean volume of hypointense areas and that of final infarcts was analyzed by the paired \( t \) test.

The mean SI\(_{pre} \), CBV\(_{p} \), and T1 and their SD were calculated. Values on the affected side were compared with values on the contralateral side. Slopes of the plot of log(SI\(_{pre} \)) versus CBV\(_{p} \) were also compared between the 2 sides. Statistical significance was determined by the paired \( t \) test across the whole patient sample. A value of \( P<0.05 \) was considered statistically significant.

**Results**

The side of hypointense area on precontrast DSC-MR image was statistically associated with the side of arterial occlusion (\( P<0.0001 \)). Figure 1 demonstrates precontrast DSC-MR image for patient 3. A hypointense area in the cortical region did not show infarction. This patient showed spontaneous recanalization 3.5 hours after the onset of neurological symptoms. This recanalization was determined on the basis of abrupt disappearance of neurological deficits at that time and later angiographic studies (Figure 1). Figure 2 shows the initial T2-weighted or CT images, precontrast DSC-MR images, and follow-up T2-weighted or CT images for the
other 5 patients. No hypointense area was seen in patient 5, and cortical regions escaped infarction. All hypointense areas seen in the other patients were finally infarcted, and mean volume of the final infarcts (26.4 ± 13.5 mL, mean ± SD) was larger than that of precontrast DSC-MR hypointensity (13.4 ± 4.5 mL) in these patients, but this tendency did not reach statistical significance (P = 0.11).

The mean S_Ipre of the affected side (432 ± 30, arbitrary units) was significantly smaller than that of the contralateral side (452 ± 32, P = 0.0001). The mean CBV p of the affected side (0.36 ± 0.18, arbitrary units) was not significantly different from that of the contralateral hemisphere (0.42 ± 0.16). The mean T1 of the affected side (776 ± 27 ms) was not statistically different from that of the contralateral side (774 ± 25 ms). The slope of the semilogarithmic plot of S_Ipre versus CBV p for the affected side (−0.043 ± 0.037) was significantly smaller than that for the contralateral side (0.039 ± 0.033, P < 0.0001).

**Discussion**

The present study demonstrated that T2*-sensitive MR imaging can detect local hypointensity in the vascular territory of the occluded cerebral artery in patients with acute ischemic stroke. The hypointensity may result from increased deoxygenation of hemoglobin in blood, indicating misery perfusion and tissue at risk for infarction.

The signal intensity of DSC-MR images depends on T1 and T2* of the tissue of interest (see Equation 1). T2* of brain tissue is a function of CBV and [dHb] (see Equation 2). Because there was no statistically significant difference in T1 and CBV p between the affected and the contralateral hemispheres in the present study, the factor contributing most to the reduction of local S_Ipre hypointensity was considered to be the increased [dHb] in the vascular territory of the occluded artery.

The origin of observed signal intensity change was further examined in a pixel-by-pixel analysis of the relationship between CBV p and S_Ipre. In this analysis, the slope of the semilogarithmic plot of S_Ipre versus CBV p for the affected hemisphere was significantly smaller than that of the contralateral hemisphere. In Equation 2, A and B depend on blood vessel architecture within a voxel.23 Because there was no significant difference in CBV p between the affected and the contralateral hemispheres, the same values of A and B can be applied for both hemispheres. Although Hct in capillaries and veins in the ischemic area was significantly lower than that in normal brain areas in experimental studies,24 R*_a decreases as Hct decreases if the other parameters in Equation 2 are fixed. The decrease in R*_a will cause an increase in S_Ipre (see Equation 1). Therefore, the decrease in the slope of the S_Ipre versus CBV p plot in the affected region was not caused by the change in Hct. B in Equation 2 is related to T2 and local heterogeneity of the magnetic field produced by sources independent of the blood oxygenation level. Because no apparent difference between the ipsilateral and contralateral hemispheres was observed on fast spin-echo T2-weighted images (Figures 1 and 2; an unavoidable partial volume effect from hypointense cerebrospinal fluid precluded quantitative ROI-based analysis for spin-echo T2-weighted images), T2 may not differ significantly between the symmetrical mirror regions of the hemispheres. (A reduction in T2, as observed in experimental studies,14 may be too small to detect on the present T2-weighted images at 1.5 T.) Local field inhomogeneity also may not differ significantly between hemispheres because of the anatomic symmetry. Thus, the decrease in the slope of the S_Ipre versus CBV p plot for the affected hemisphere probably is due to an increase in [dHb]. This further confirms that the hypointense signal in T2*-sensitive MR images of the affected hemisphere was induced by the elevated deoxyhemoglobin level of the circulating blood.

Brain lesions associated with hypointense T2*-sensitive images became infarcted in all but patient 3. One patient with a normal T2*-weighted image escaped infarction. The increased OEF, corresponding to the hypointense T2*-sensitive image, has been studied by means of PET in relation to the evolution of infarction. Marchal et al25 investigated OEF in acute stroke patients. In their study, an increased OEF (0.753 ± 0.152) was found up to 17 hours after stroke onset. The cerebral metabolic rate of oxygen (CMRO2) ranged from 1.55 to 2.23 mL · 100 g⁻¹ · min⁻¹, which is well above the value of 1.30 mL · 100 g⁻¹ · min⁻¹ accepted as the CMRO2 threshold for infarction.26 The lesions in their patients, however, evolved into infarction at the chronic stage. Several studies also demonstrated metabolic derangement and evolution of infarction in brain regions with increased OEF during the subacute and chronic stages.6,7 Thus, an increased OEF or a hypointense T2*-sensitive image may indicate a high risk of infarction, although an increased OEF by itself may not be an accurate predictor of the occurrence of infarction.5 In several animal experiments, however, infarction was prevented or reduced in size when the occluded artery was reopened.3,27 These findings and the experience of our patient 3 indicate that brain regions demonstrating a hypointense signal on a T2*-sensitive image may be a target for acute therapy to improve compromised cerebral circulation.

There are 2 different situations in the misery perfusion syndrome.1 One is a chronic syndrome in patients with severe carotid artery disease in whom a modest reduction in CBF is associated with normally maintained oxygen metabolism. This may persist for a long period of time. The other is an acute syndrome in patients with brain embolism investigated in this study in which the tissue is undergoing the process of infarction.5–7 It remains unproven that the T2*-sensitive MR imaging can detect hypointensity related to blood deoxygenation in chronic misery perfusion syndrome.

There were several limitations to T2*-sensitive MR imaging in detecting brain areas containing deoxygenated blood. As noted previously, susceptibility artifact from air interfered with the detection of true signal change. Side-by-side comparison was done to identify hypointense signal intensity in T2*-sensitive images. This is not appropriate in patients with coexisting brain lesions, however. The signal intensity of T2*-sensitive images is influenced by the pathological nature of the tissue (eg, hemosiderin deposition, leukoaraiosis, and old infarction) represented by B in Equation 2. The OEF of PET, an indicator of misery perfusion, is quantitative, but the
hypointense signal intensity of T2*-sensitive images is qualitative at present.

Despite these limitations, DSC-MR T2*-sensitive images before the first arrival of contrast medium to the brain may be valuable in identifying misery perfusion previously detected only by PET. It should be analyzed in relation to ischemic penumbra determined by a mismatch between perfusion and diffusion in MR study. Further validation of T2*-sensitive MR imaging compared with PET OEF study in a larger patient population is needed.

In conclusion, our data suggest that use of DSC-MR images before the arrival of the contrast agent enables detection of hypointensity caused by deoxygenation in the affected cerebral hemisphere of acute ischemic stroke patients. Such hypointensity may be an index of misery perfusion and may provide useful information for the determination of appropriate patient therapy. These preliminary data describe a relative and not yet quantifiable index of oxygen extraction, the relevance of which must be proven compared with diffusion and perfusion MRI and with quantitative PET studies.

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References
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