Regional Ischemia and Ischemic Injury in Patients With Acute Middle Cerebral Artery Stroke as Defined by Early Diffusion-Weighted and Perfusion-Weighted MRI

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Background and Purpose—We sought to map early regional ischemia and infarction in patients with middle cerebral artery (MCA) stroke and compare them with final infarct size using advanced MRI techniques. MRI can now delineate very early infarction by diffusion-weighted imaging (DWI) and abnormal tissue perfusion by perfusion-weighted imaging (PWI).

Methods—Seventeen patients seen within 12 hours of onset of MCA stroke had MR angiography, standard MRI, and PWI and DWI MRI. PWI maps were generated by analysis of the passage of intravenous contrast bolus through the brain. Cerebral blood volume (CBV) was determined after quantitative analysis of PWI data. Volumes of the initial DWI and PWI lesion were calculated and compared with a final infarct volume from a follow-up imaging study (CT scan or MRI).

Results—Group 1 (10 patients) had MCA stem (M1) occlusion by MR angiography. DWI lesion volumes were smaller than the volumes of CBV abnormality. In 7 patients the final stroke volume was larger or the same, and in 3 it was smaller than the initial CBV lesion. Group 2 (7 patients) had an open M1 on MR angiography with distal MCA stroke. In 6 group 2 patients, the initial DWI lesion matched the initial CBV abnormality and the final infarct.

Conclusions—Most patients with M1 occlusion showed progression of infarction into the region of abnormal perfusion. In contrast, patients with open M1 had strokes consistent with distal branch occlusion and had maximal extent of injury on DWI at initial presentation. Application of these MRI techniques should improve definition of different acute stroke syndromes and facilitate clinical decision making. (Stroke. 1998;29:939-943.)

Key Words: middle cerebral artery ■ stroke ■ magnetic resonance imaging ■ diffusion-weighted imaging ■ perfusion-weighted imaging

The MCA is the artery most commonly affected in human strokes. There is considerable variability in the extent and location of infarction in patients with embolic MCA territory stroke. Two major patterns emerge: (1) occlusion of the MCA stem with (a) a large infarct involving both the deep territory supplied by lenticulostriate penetrator vessels and the cortex supplied by the major divisions of the MCA or (b) readily available adequate leptomeningeal collateral flow, in which case the cortex survives but the deep territory supplied by the poorly collateralized M1 penetrators proceeds to infarction, or (2) an open MCA stem with emboli that pass distal to the origin of the penetrators. Infarction may involve only the territory supplied by a single division or a small cortical branch. Functional outcome and treatment decision should depend on which of the above patterns are operative.

Accurate clinical discrimination between different patterns of MCA stroke is difficult, and new MRI techniques promise to improve diagnosis of the extent and location of infarct in the emergency setting. DWI has been shown to be sensitive to early ischemic injury in the brain,1,2 while alteration in blood flow can be appreciated with PWI.3 Combined DWI/PWI permits new pathophysiological insight in the setting of acute stroke4,5 because it allows regional assessment of both ischemic and irreversibly damaged or infarcted brain tissue. We used these new tools to map early regional infarction and ischemia in patients with MCA stroke. We hypothesize that whereas the pattern of ischemia and infarction depends on the site of the obstructed vascular lesion, DWI/PWI techniques allow a prediction of final infarct size along a continuous scale.

Subjects and Methods

Patients who had symptoms and signs of an MCA territory stroke between July 1994 and April 1996 and had an acute stroke protocol MRI within 12 hours from the onset of their deficit were analyzed. Seventeen consecutive patients were identified. Nine of these 17 patients were previously described in an initial report on DWI/PWI...
Selected Abbreviations and Acronyms

CBV = cerebral blood volume
DWI = diffusion-weighted imaging
MCA = middle cerebral artery
MRA = magnetic resonance angiography
PWI = perfusion-weighted imaging
rCBV = regional cerebral blood volume

in acute stroke. Patients underwent MRI 1.5 to 10 hours after the onset of symptoms. The initial diagnosis of MCA territory infarct was confirmed in all 17 patients by the acute MRI as well as on follow-up clinical and imaging examinations. In all 17 patients DWI and PWI depicted distinct abnormalities in the acute phase that predicted infarction location on follow-up conventional CT and/or MRI done 3 to 7 days later. All patients were treated in a similar fashion, including the use of intravenous anticoagulation. Anticoagulation was started before the DWI/PWI was performed.

As reported, our acute stroke protocol MRI includes sagittal T1, axial T2, proton density of fluid-attenuated inversion-recovery imaging (FLAIR), DWI, circle of Willis two-dimensional phase-contrast MRA, postgadolinium T1, and PWI. MRI is performed with the use of a General Electric Signa 1.5-T MRI unit with an echo-planar retrofit from Advanced NMR Systems. The protocol requires approximately 30 minutes.

Our DWI technique samples the entire diffusion tensor. The technique consists of six high- b value single-shot images at each slice position, each corresponding to diffusion measurement in a given direction, followed by a single low- b value image. The high b value we use is 1221 s/mm²; the low value is 3 s/mm². A summary of the parameters is as follows: repetition time, 6 seconds; echo time, 118 milliseconds; matrix, 256×128; field of view, 40×20 cm; slice thickness, 6 mm; interslice gap, 1 mm. The complete seven-image tensor acquisition requires 42 seconds; we typically acquire three repetitions to improve the signal-to-noise ratio, which results in a total imaging time of 126 seconds. Generation of isotropic (tensor trace) DWI occurs off-line on a networked workstation (Sparcstation 20, Sun Microsystems) and requires 5 to 10 minutes for data transfer and computation.

Qualitative perfusion imaging is obtained by performing spin-echo echo-planar imaging during the rapid intravenous injection of 0.2 mmol/kg of gadodiamide or gadopentetate. We obtained 51 complete single-shot echo-planar images (repetition time, 1500 milliseconds; echo time, 75 milliseconds) in each of 10 slices for a total of 510 complete images acquired in 77 seconds, or 46 single-shot echo-planar images in each of 11 slices for 506 complete images acquired in 69 seconds. Data were then transferred to a workstation for further analysis. Perfusion scans were analyzed for regional abnormalities on the rCBV maps, as previously described.

Two-dimensional phase-contrast angiography was performed. Imaging of three 10-mm-thick sections through the region of the circle of Willis was performed, with an encoding velocity of 80 cm/s.

Lesion volume was calculated with a planimetric technique for DWI, T2, and PWI scans and the follow-up study. The outline of the abnormality was first obtained with the use of a semiautomated segmentation technique in a commercial image analysis package (Alice; Hyden Image Processing). The outlined abnormality was then modified by a research assistant to fit the lesion by eye in each slice independently. These were then confirmed or corrected by a neuroradiologist and a neurologist. The area of the abnormality on each section was multiplied by the section thickness plus the gap between slices to obtain a volume measurement. All MRI techniques were performed in the same section plane and location to minimize volume-averaging errors.

The distribution of the abnormality on the acute DWI and CBV maps and on the follow-up studies was categorized as involving one or more of the following territories: deep lenticulostriate territory; anterior cerebral artery/MCA territory watershed (supraventricular white matter of the centrum semiovale and cortical borders between the anterior cerebral artery and MCA territories); MCA superior and/or inferior division; or small surface branch.

Statistical analyses were done with the use of the Wilcoxon test for categorical variables and linear regression analysis for continuous variables.

Results

Seventeen consecutive patients with symptoms and signs of an MCA territory stroke underwent the acute stroke protocol MRI between July 1994 and April 1996.

We were able to separate the patients into two groups based on the MRA results. Ten patients (group 1) had M1 occlusion by MRA, and 7 patients (group 2) had a normal-appearing flow signal in the M1 segment on MRA. In all group 1 patients the final infarction volume was larger (Table) than the initial DWI lesion. In 6 of 10 patients the lesion size more than doubled. Initial DWI lesion volumes were smaller than the volume of CBV abnormality in all but 3 patients (patients 4, 8, and 15). Final infarct volume was smaller than the initial CBV abnormality in 3 patients (patients 3, 7, and 9) and was of similar size in 2 (patients 5 and 11). In the remaining 5 patients the final stroke volume exceeded the initial CBV lesion volume. In 3 of the group 2 patients (Table) the initial DWI lesions matched the final infarct size (patients 1, 12, and 17), and in 2 (patients 6 and 16) the final infarct sizes were close to the volumes of the initial DWI lesions. In 1 patient (patient 6) the stroke size was so small that the apparent shrinkage in size could be related to measurement variability since slice position was not identical on the follow-up scan. Only 1 patient (patient 14) had a major increase in stroke size (Table). This patient likely had a second vascular event after his initial DWI and PWI scans. The first scan showed a superior division territory abnormality, whereas the follow-up study showed a complete MCA and posterior cerebral artery stroke.

There was no difference in the mean initial DWI lesion size between groups 1 and 2 (49.7±20 versus 15.1±16 cm³; P>0.15). Between groups 1 and 2 there were significant differences in the size of the initial CBV abnormality (83.3±16 versus 8.1±20 cm³; P<0.005) and the size of the final stroke (108.6±22 versus 23.9±27 cm³; P<0.003). Both the initial DWI abnormality and the initial CBV size correlated significantly with final stroke size (r²=0.74 and .84, respectively; P<0.0001 for both), with a better correlation for the initial CBV abnormality. It should be noted that final stroke size was always measured on a scan 3 to 7 days (mean, 6 days) after the initial event, and the contribution of ischemic edema to stroke volume is unknown. The T2 abnormality appeared to match the DWI abnormality in all cases by this time. None of the included cases had clinically evident malignant brain edema or major mass effect on imaging. However, some contribution of ischemic edema to the stroke volume measurement on the follow up scan is likely. A third image at or around 2 weeks from onset would be required to detect and measure this effect.

There were three different patterns of DWI/PWI in acute MCA stroke in patients with an occluded MCA stem (group 1). Two patients (patients 5 and 8) had early complete MCA territory infarction (Figure 1). Five patients had extensive...
ischemia with progressive infarction starting in the peri-insular region (group 1; patients 2, 4, 10, 11, and 15) (Figure 2). Three patients had MCA flow obstruction with DWI abnormalities in the lenticulostriate territory and cortical ischemia on PWI but never developed evidence of cortical injury (group 1; patients 3, 7, and 9) (Figure 3).

<table>
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<tr>
<th>Pt No.</th>
<th>Age/Sex</th>
<th>Time From Ictus, h</th>
<th>DWI Size, cm³</th>
<th>CBV Size, cm³</th>
<th>F/U Size, cm³</th>
<th>ICA/MCA Occlusion/Status*</th>
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Pt indicates patient; F/U, follow-up; and ICA, internal carotid artery.

*Oclusion refers to group 1; status refers to group 2.

Five patients in group 2 had a cortical branch stroke with matching DWI and PWI abnormalities (patients 1, 6, 12, 16, and 17) (Figure 4), while one patient had ischemia in both MCA divisions with abnormal DWI initially limited to one
division; on the following scan the territory of the spared division was recruited into the infarct (patient 13).

**Discussion**

After cerebrovascular occlusion the transition from reversible ischemia to irreversible damage is a process that occurs at a variable rate dependent on the degree of ischemia. Recent positron emission tomography and functional MRI studies have reported that potentially viable tissue persists in some ischemic stroke patients in the peri-infarct region for the first 24 to 48 hours after stroke onset. A technique that could delineate irreversibly damaged tissue from ischemic but viable brain would greatly assist present and future treatment decisions that involve thrombolytic or neuroprotective drugs.

PWI and DWI can depict focal cerebral ischemia and irreversible ischemic injury, respectively, in the very early stages of stroke, earlier than can be depicted with conventional CT or MRI. We and others have reported that the region of infarcted tissue as demonstrated by the initial DWI abnormality can enlarge into a larger volume of brain hypoperfusion demonstrated by decreased rCBV on the initial perfusion scans. The mismatch between the region of hypoperfusion (larger) and the region of diffusion abnormality (smaller) may predict those patients at risk for infarct enlargement.

Human ischemic stroke is a heterogeneous entity caused by a variety of pathophysiological mechanisms with different profiles and outcomes. MCA territory infarction is the most common arterial territory affected in major stroke syndromes. We demonstrate for the first time using functional MRI methods that MCA stroke can be classified into clinically and pathophysiologically important different subtypes on the basis of MRA, PWI, and DWI.

In our study patients with M1 occlusion usually showed progression of infarction into a larger region of abnormal perfusion in the hours or days after initial presentation. These patients had a mismatch between the extent of early infarction (DWI abnormal) and extent of early ischemia (PWI abnormal). We were able to demonstrate in this group that the early CBV abnormality is slightly better than the DWI abnormality as a predictor of final infarct size. Patients with these radiological characteristics may represent the group most likely to benefit from reperfusion therapy. One subgroup of the patients with M1 occlusion showed progression of infarction limited to the poorly collateralized lenticulostriate territory (Figure 3). In such patients, cortical regions demonstrated abnormal PWI but normal DWI. The ischemic cortex in such patients may or may not survive, depending on the degree and duration of ischemia, and constitutes ischemic brain at risk. Other patients showed an early ischemic injury in the perinsular cortex, which then spread into other cortical areas (Figure 2). The peri-insular cortex may be especially susceptible because of relatively poor collateral flow since it is located most distal to the leptomeningeal collaterals. A third group of patients with MCA occlusion presumably without collateral flow had rapid evolution of infarction in the entire territory of ischemia (Figure 1). This heterogeneity could also, at least in part, relate to the duration of occlusion and timing of spontaneous recanalization. Although extension of
infarction appears to play a major role in enlargement of the region of injury, the contribution of ischemic edema leading to overestimation of final stroke size or tissue loss leading to underestimation needs to be further investigated.

In contrast to group 1, patients with flow-related signal enhancement in the MCA stem and stroke location and size consistent with distal branch occlusion were found to have maximal extent of regional injury on their initial study (matched DWI/CBV) (Figure 4). Unless neuroprotective or reperfusion agents can be shown to reverse DWI abnormalities, then in these patients, as well as in those with M1 occlusion and rapid evolution of DWI injury path through the entire ischemic territory, such therapies may not be justified.

The appearance of the MCA stem on MRA provides indirect information and can help to predict final infarct size. These new functional MRI techniques can directly measure parameters in an individual patient that not only predict final infarct size but, by demonstrating mismatch between ischemia (regions of rCBV abnormality) and already injured tissue (regions of abnormality on DWI), define possible salvageable tissue.4,5

The ability to demonstrate the extent of the ischemic penumbra, defined as ischemic brain tissue at risk for infarct but still potentially recoverable,10,11 is crucial because it constitutes the target for early therapy. It is also crucial to recognize those patients who have already sustained the maximal extent of ischemic injury and do not have brain tissue at risk for further infarct to avoid exposing them to the potential risks of thrombolysis and neuroprotective agents.

In conclusion, combined DWI and PWI in the acute setting can help to identify brain tissue already injured or ischemic and still at risk for infarction. With the help of these new imaging techniques, the pattern of acute MCA stroke can be defined more clearly. This information may help us to more accurately select those patients who should receive thrombolytic and neuroprotective therapies.

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References
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