Reversible Focal Ischemic Injury Demonstrated by Diffusion-Weighted Magnetic Resonance Imaging in Rats

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Background and Purpose: Diffusion-weighted magnetic resonance imaging (DWI) can quantitatively display focal brain abnormalities within minutes after the onset of ischemia. We performed the present study to determine the effects of 1 and 2 hours of temporary ischemia on DWI.

Methods: We examined DWI and T2-weighted magnetic resonance images (T2WI) during and after 1 and 2 hours of temporary middle cerebral artery occlusion in rats (n=10 for each group). In a subgroup of four animals from each group, we employed perfusion magnetic resonance imaging to monitor cerebral perfusion. Neurological outcome and infarct size after survival for 24 hours were compared between the groups and correlated with DWI and T2WI studies.

Results: Perfusion studies qualitatively documented hypoperfusion and reperfusion during and after temporary occlusion. Lesion size on DWI during reperfusion was significantly less than that during ischemia for 1 (55% decline, p<0.02) but not 2 hours of occlusion. The DWI signal intensity ratio (intensity compared with that in the contralateral homologous area) just before withdrawal of the occluder was significantly less in regions where the hyperintensity disappeared after withdrawal than in regions with persistent hyperintensity (p<0.002). The T2WI studies revealed few or no abnormalities, except after 2 hours of occlusion. The neurological outcome was significantly better in the 1-hour than in the 2-hour group (p<0.05). Postmortem infarct volume was significantly smaller in the 1-hour group than in the 2-hour group (p<0.05). The postwithdrawal DWI accurately predicted infarct size (R=0.96, p<0.0001).

Conclusions: The present study indicates that DWI can rapidly display not only irreversible but also reversible ischemic brain damage and enhances the importance of DWI as a diagnostic modality for stroke. (Stroke 1992;23:1304-1311)

KEY WORDS • cerebral ischemia • magnetic resonance imaging • reperfusion • rats

The development of infarction depends primarily on the severity and duration of ischemia.1,2 Ischemic brain injury may recover if blood flow is restored after a brief period of ischemia.3-7 This concept has led to several therapeutic attempts to restore blood flow in animal stroke models and in human stroke by using thrombolytic therapy.8,9 However, if irreversible ischemic injury has already occurred, reperfusion of the ischemic tissue will not be useful and may be hazardous because reperfusion could exacerbate brain edema or promote hemorrhagic transformation.8-11

Efforts to distinguish reversible from irreversible brain damage in experimental and clinical stroke have led to the concept of the ischemic penumbra.12,13 However, it has been difficult to differentiate salvageable tissue from irreversibly damaged tissue. Positron emission tomography may provide useful information concerning tissue viability,14 but this technique has several disadvantages, including cost, manpower, examination time, and invasiveness. X-ray computed tomography and standard magnetic resonance imaging (MRI) with T1- and T2-weighted images (T2WI) cannot detect ischemic lesions for hours after the onset of ischemia.15,16 Diffusion-weighted MRI (DWI) can display regions of ischemic injury within minutes after onset.17-19 Differences in the apparent diffusion coefficient (ADC) of water protons, reflecting molecular translational movement (Brownian motion) of water molecules, generate contrast in DWI.20-22 Regions of reduced water molecule motion appear hyperintense. In ischemic lesions, a rapid failure of energy metabolism and associated ion pumps leads to the accumulation of sodium ions (Na+) and water within ischemic cells (cytotoxic edema).23-25 Hyperintense areas displayed on DWI soon after an ischemic insult may represent cytotoxically injured brain tissue, which can be rapidly and accurately identified using DWI.

See Editorial Comment, p 1310

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toxic edema formation in ischemic tissue.\textsuperscript{17} Our previous study demonstrated that DWI displays hyperintense areas, encompassing most of the middle cerebral artery (MCA) territory, 30 minutes after suture MCA occlusion in rats and that the size of the hyperintense area is highly correlated with that of infarction demonstrated with 2,3,5-triphenyltetrazolium chloride (TTC) staining after survival for 24 hours.\textsuperscript{19} In a similar MCA occlusion model in rats, regions of DWI hyperintensity revert to normal if the occluder is removed from the intracranial artery 33 minutes after occlusion.\textsuperscript{18} These observations indicate that DWI studies soon after arterial occlusion accurately predict the ultimate area of infarction, but early DWI abnormalities in part represent reversibly damaged tissue that may improve with appropriate intervention.

Dynamic contrast-enhanced perfusion MRI, using multiple, repetitive, ultrafast imagings combined with the intravenous injection of a paramagnetic or super-paramagnetic contrast agent, can monitor a transient decrease in T2*-weighted signal intensity caused by a strong contrast agent–induced field gradient between the capillary space and surrounding tissue and can evaluate the cerebral perfusion state.\textsuperscript{26,27} We performed the present study using a rat intraluminal suture MCA occlusion model to determine the effects of 1 and 2 hours of temporary MCA occlusion on serial changes in early DWI and T2WI, perfusion MRI, neurological outcome, and postmortem infarct size at 24 hours.

Materials and Methods

We studied 20 adult male Sprague-Dawley rats weighing 280–370 g. Our procedures were approved by the Animal Research Committee of the University of Massachusetts Medical School (ARC Protocol #A-643). Two groups of 10 rats each were randomly assigned to temporary occlusion of the MCA for 1 or 2 hours. Animals were anesthetized with 400 mg/kg body wt i.p. chloral hydrate. Polyethylene catheters were introduced into the left femoral artery and into the vena cava through the left femoral vein. The rat’s body temperature was maintained close to 37.0°C with a heat lamp during the operation.

We used a modified intraluminal suture MCA occlusion model described in detail previously.\textsuperscript{19} Briefly, an intraluminal occluder, 4-0 monofilament nylon suture with its tip rounded by flame heating, was introduced through the right common carotid artery (CCA) into the internal carotid artery, then advanced intracranially approximately 17 mm from the CCA bifurcation. With this procedure, the intraluminal suture occludes the origin of the MCA.\textsuperscript{19,28–30} Restoration of perfusion to the ischemic tissue was accomplished by pulling the occluder back to the CCA.

Four rats in each group were subjected to experiment A, perfusion MRI and DWI studies. DWI and perfusion MRI studies were performed 30 and 15 minutes before withdrawing the occluder, respectively. Perfusion MRI studies were repeated 15 minutes after withdrawing the occluder and were followed by DWI and T2WI studies 30 minutes after withdrawal. The other six rats in each group were examined only with serial DWI and T2WI studies to analyze sequential changes in the area and degree of hyperintensities (experiment B). Initial DWI and T2WI studies were performed at 30 minutes in the 1-hour group. In the 2-hour group, MRI studies were obtained 30, 60, and 90 minutes after arterial occlusion. After withdrawal of the occluder, DWI and T2WI studies were repeated at 30-minute intervals for 120 (1-hour group) or 90 (2-hour group) minutes.

Each rat was placed in the prone position, fixed to a bird-cage radiofrequency coil, and anesthetized with 0.5–1.0% isoflurane during the imaging protocol. Body temperature was kept close to 37.0°C with a water-circulating heating pad (K-module model K-20, American Pharmescal, Valencia, Calif.).\textsuperscript{19} Arterial blood pressure was monitored continuously, and a 0.5-ml aliquot of arterial blood was collected for measuring blood gases at baseline, before MCA occlusion, and 20 and 180 minutes after MCA occlusion.

The MRI studies were performed in a General Electric CSI-II 2.0-T/45-cm imaging spectrometer (GE Co., Fremont, Calif.) equipped with self-shielded gradient coils capable of producing a maximum field strength of \( \pm 20 \) G/cm. Before the formal MRI studies, preview spin/echo images were obtained to determine exact slice planes. Dynamic contrast-enhanced perfusion MRI studies were performed at a coronal slice with a thickness of 2 mm, involving the optic chiasm (chiasmatic slice), using echo-planar imaging (EPI).\textsuperscript{31} EPIs were acquired at 1-second intervals over 16 seconds immediately after a bolus injection of 0.3 ml physiological saline containing 0.05 mmol superparamagnetic iron oxide particles/kg iron (AquaMag 100 magnetic fluid, catalog No. 4180, Advanced Magnetics, Inc., Cambridge, Mass.) via an intravenous catheter over 1 second.\textsuperscript{27,32} The EPIs were acquired using an incarnation of the EPI sequence in which the whole k-space is scanned in a “sawtooth” pattern.\textsuperscript{31} A set of imaging data was acquired in 65.5 msec, with a repetition time (TR) of 1 second. DWI and T2WI were also obtained at the same slice position. In experiment B, MRI signals were recorded from four slices, and the chiasmatic slice was selected for further analysis. DWIs were collected over 8 minutes with a TR of 1,800 msec, an echo time (TE) of 45 msec, and half-sine–shaped diffusion-sensitive gradient pulses with a duration of 10 msec, a pulse separation of 20 msec, and strength of 15 G/cm, yielding a \( b \) value of 1,142 sec/mm\(^2\). T2WIs with a TR of 2,200 msec and a TE of 90 msec were obtained over 10 minutes.\textsuperscript{19}

After the MRI protocols, the rats were permitted to recover from the anesthesia. Neurological evaluation was performed 24 hours after the induction of ischemia and scored on the following six-point scale, which was modified from the scale proposed by Zea Longa et al.\textsuperscript{33} 0, no neurological deficit; 1, failure to extend left forepaw fully; 2, circling to the left; 3, falling to the left; 4, no spontaneous walking with a depressed level of consciousness; and 5, dead. Then the animals were anesthetized with 300 mg/kg i.p. chloral hydrate and decapitated. The brains were quickly removed, sectioned coronally at 2-mm intervals, stained with a 2\% TTC solution at 37°C for 30 minutes,\textsuperscript{33} and fixed by immersion in a 10\% phosphate-buffered formalin solution. The six brain sections per animal stained with TTC were photographed with a 35-mm camera mounted on a surgical microscope after 48 hours of formalin fixation.

Data from perfusion MRI, DWI, T2WI, and TTC studies were blindly analyzed by an observer unaware of the group and of the study time point. The perfusion
state in the MCA territory as determined with perfusion MRI studies was qualitatively graded (perfusion scale) as 0, no difference from the contralateral MCA territory; 1, delayed transit of the contrast agent as evidenced by slower decline and recovery in signal intensity than in the contralateral MCA territory; 2, part of the MCA territory had an incomplete decline in signal intensity; 3, the entire MCA territory had an incomplete decline in signal intensity; and 4, no decline in signal intensity in the entire MCA territory. Images from DWI and T2WI studies were photographed after modifying window levels to contrast the hyperintense areas with background normal tissues. The enlarged photographs were evaluated with a computer-assisted digitizer (Sigma-Scan V3.10, Jandel Scientific, Corte Madera, Calif., and Numonics 2200, Numonics Corp., Montgomeryville, Pa.). The border of the hyperintense area was visually judged and traced. The area of the hyperintense region was divided by the area of the ipsilateral hemisphere to obtain the percent hemispheric lesion area (%HLA). Photographs of TTC-stained sections were similarly evaluated using the digitizer to determine %HLA. Areas not stained red were considered as infarcted. The infarct volume (in cubic millimeters) was calculated by using numerical digitizer to determine %HLA. Areas not stained red were considered as infarcted. The infarct volume (in cubic millimeters) was calculated by using numerical integration of the lesion areas for all TTC sections per rat and the distances between them. Only in animals for experiment B, the degree of DWI hyperintensity was evaluated using the signal intensity ratio (SIR), the average signal intensity within the region of interest (ROI) (1.0×1.0×2.0 mm³) divided by that in the contralateral, nonischemic, homologous region. SIR was calculated in three ROIs (caudoputamen, frontaloparietal cortex, and temporal cortex) for each rat. ROIs with DWI hyperintense areas demonstrated only during occlusion were defined as reversible and those with areas of persistent hyperintensity as irreversible. SIR values were compared between reversible and irreversible ROIs for each DWI study time point. Animals in experiment A were not used for analyzing SIR because of the potential decrease in signal intensity caused by iron particles circulating in the blood.

For comparison of parametric variables, analysis of variance was used. Wilcoxon and Mann-Whitney tests were applied for comparison of paired and unpaired nonparametric data sets, respectively. Because distributions of observed values for %HLA and infarct volume differed from a normal distribution, these values were also analyzed with the nonparametric methods. For comparison of the observed frequencies in multiple categories, contingency table analysis was used. Linear regression analysis was used for correlating parametric data sets. For assessing correlation of the nonparametric graded scales with other variables, Spearman’s rank correlation coefficient analysis was applied. All values presented are mean±SEM. A two-tailed probability value of less than 0.05 was considered significant.

Results

No significant differences between the groups were observed in any physiological measurement (data not shown) except PCO₂, which declined after the onset of occlusion in both groups (p=0.0076). All rats except one in each group survived for 24 hours after MCA occlusion. The animals that died just before 24 hours were scored as 5 on the neurological grading scale, then their brains were immediately subjected to TTC staining. The neurological scale score at 24 hours was 1.0±0.6 in the 1-hour group, significantly better than the value in the 2-hour group (2.7±0.5, p<0.05).

In all rats in experiment A, perfusion MRI studies during occlusion demonstrated hyperperfusion in the right MCA territory (perfusion scale grade of 3.50±0.27; Figure 1, top). The perfusion scale grade was significantly correlated with prewithdrawal DWI %HLA (R_{Spearman}=0.866, p<0.025). The perfusion abnormalities improved after withdrawal of the occluder in all animals (perfusion scale grade 0.88±0.35, p<0.02; Figure 1, bottom). Perfusion scale grades before and after withdrawal of the occluder in the 1-hour group (data not shown) were not different from those in the 2-hour group.

The 30-minute DWI study demonstrated a hyperintense area in both the caudoputamen and the neocortex (Figure 2, top). There were no significant differences in 30-minute %HLA between the groups (Table 1). In four rats in the 1-hour group, the DWI hyperintensity disappeared completely 30 minutes after withdrawal of the occluder. Three animals had hyperintensity in the caudoputaminal region alone (Figure 2, bottom), and the other three had a persistent hyperintensity in both the caudoputamen and the neocortex. The DWI %HLA obtained 30 minutes after withdrawal of the occluder was significantly smaller than the prewithdrawal value (55% decline, p<0.02). In the 2-hour group, the 90-minute (prewithdrawal) %HLA was almost identical to that at the 30-minute study. An only 17% decline in %HLA was observed 30 minutes after withdrawal of the occluder (not significant), and DWI hyperintensity was still noted in the caudoputamen and neocortex in nine rats. The postwithdrawal DWI lesion size did not change during the observation period in either group. No significant differences in DWI %HLA between animals in experiments A and B were noted during the prewithdrawal or postwithdrawal periods.

The T2WI studies did not demonstrate any obvious change in signal intensity during occlusion in either group. Among the six 1-hour occluded rats with infarcts as demonstrated with the TTC study, only one had a well-defined hyperintense area after withdrawal of the occluder. In the 2-hour group, postwithdrawal T2WI studies frequently revealed hyperintensity in the MCA territory, and the hyperintense areas were almost comparable to the %HLA in DWI and TTC studies in seven animals. Postwithdrawal T2WI %HLA was 6.4±3.3% in the 1-hour group and 33.2±5.2% in the 2-hour group (p<0.001).

As shown in Table 1, TTC %HLA was significantly smaller in the 1-hour group than in the 2-hour group (p<0.05). Infarct volume in the 1-hour group was 81.1±38.2 mm³, significantly smaller than the 178.8±31.7 mm³ observed in the 2-hour group (p<0.05). Infarcts on the TTC-stained sections were almost identical in location and size to DWI hyperintense areas after withdrawal. Postwithdrawal DWI %HLA correlated with TTC %HLA (R=0.96, p<0.0001; Figure 3), indicating that DWI after withdrawal of the occluder accurately predicts infarct size at postmortem examination.

Among the 36 ROIs available for SIR determination, five had no DWI abnormalities throughout the study.
FIGURE 1. Perfusion magnetic resonance imaging studies during and after 2 hours of temporary middle cerebral artery (MCA) occlusion in rats. Coronal, echo-planar T2-weighted images at chiasmatic slice were obtained at 1-second intervals immediately after bolus injection of superparamagnetic contrast agent. Left upper, right upper, left lower, and right lower images were obtained 0, 1, 2, and 3 seconds after injection, respectively. Top: During arterial occlusion, rapid and significant decline in signal intensity was observed in all areas except right MCA territory. In almost the entire territory of the occluded MCA signal intensity did not noticeably decline (perfusion scale grade of 3), indicating moderate hypoperfusion. Bottom: Immediately after withdrawal of occluder, signal was attenuated from entire brain, including previously hyperintense right MCA territory (perfusion scale grade of 0), indicating normal perfusion in previously occluded MCA territory.

Period. Among the other 31 ROIs, 14 were reversible and the remaining were irreversible. SIR just before withdrawal of the occluder was 1.186±0.027 in the reversible ROIs, significantly less than the value in the irreversible ROIs (1.397±0.052, p<0.002). SIR in the irreversible ROIs increased over time after withdrawal
FIGURE 2. Typical diffusion-weighted magnetic resonance imaging (DWI) study of optic chiasm slice during and after 1 hour of temporary middle cerebral artery (MCA) occlusion in rats. Top: DWI 30 minutes after arterial occlusion demonstrated hyperintense area encompassing entire right MCA territory. Note that lesion in lateral caudoputamen was more hyperintense than lesion in neocortex. Bottom: After withdrawal of occluder, neocortical DWI hyperintensity disappeared but persistent hyperintensity was observed in caudoputamen.

Discussion

Several experimental studies indicate that DWI can display ischemic lesions soon after arterial occlusion. Reversible ROIs were observed more frequently in the 1-hour group (10 reversible and five irreversible) than in the 2-hour group (four and 12, respectively; \( p<0.05 \)).

Table 1. Lesion Size in DWI and TTC Studies in Rats

<table>
<thead>
<tr>
<th>Duration of ischemia</th>
<th>n</th>
<th>30 minutes</th>
<th>Before withdrawal of occluder</th>
<th>After withdrawal of occluder</th>
<th>TTC (24 hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 hour</td>
<td>10</td>
<td>52.8±5.4</td>
<td>52.8±5.4</td>
<td>23.8±9.6†</td>
<td>23.3±9.0†</td>
</tr>
<tr>
<td>2 hours</td>
<td>10</td>
<td>59.6±3.9§</td>
<td>58.7±5.7</td>
<td>48.7±7.2</td>
<td>52.1±7.0</td>
</tr>
</tbody>
</table>

Values are mean±SEM % hemispheric lesion area. DWI, diffusion-weighted magnetic resonance imaging; TTC, 2,3,5-triphenyltetrazolium chloride staining.

\( \ast p<0.02 \), \( \ast \ast p<0.01 \) different from before withdrawal by Wilcoxon signed rank test.

\( \ast p<0.02 \), \( \ast \ast p<0.01 \) different from 2-hour group by Mann-Whitney U test.

\( \ast \ast =6 \) (rats in experiment A are not included).
colleagues speculated that the drop in ADC resulting in DWI hyperintensity is related to cytotoxic edema. Acute energy and ionic failure, which results in cytotoxic edema, does not per se indicate irreversible damage and may in part recover even after prolonged ischemia. Local hyperthermic effects, changes in tissue osmolality, and the lack of pulsatile flow in occluded vessels are other possible, but less likely, factors affecting the ADC of water protons soon after the onset of ischemia. We cannot exclude the contribution of these factors in the appearance and reversal of DWI hyperintensity.

The present study suggests that the potential for reversal of DWI hyperintensity after withdrawal of the occluder can partly be predicted by prewithdrawal SIR. This result may imply less reduction in water diffusion in reversible lesions because ADC is the most important determinant of DWI signal intensity. SIR assessments of DWI reversibility, however, may be complicated by changes in other MRI parameters such as T1, T2, and proton density. These parameters do not account for DWI signal intensity during the early ischemia-reperfusion period, but this may not be true later. Increases in proton density and T2 prolongation probably contributed to T2WI hyperintensity after withdrawal in the 2-hour group and possibly to further increases in SIR on DWI in the irreversible ROIs. DWI signal intensity is vulnerable to motion artifact and varies depending on the gradient b value. The acquisition of ultrafast diffusion studies allows for the rapid calculation of ADC at each pixel, which should provide a better indicator for reversibility of ischemic tissue injury than SIR.

In rat MCA occlusion models, reestablishing blood flow into ischemic regions is difficult and can reliably be done in only a few models. Selman et al reported that a significant recovery in energy metabolism was noted in a 1-hour temporary occlusion group but not in a 2-hour group. Kaplan et al investigated the effects of various durations of temporary arterial occlusion in spontaneously hypertensive rats on the neocortical infarct volume at 24 hours. These authors found that focal ischemia for 1 hour caused little or no infarction, while ischemic intervals of 2 and 3 hours produced larger volumes of infarcted tissue. In a study using a rat intraluminal suture MCA occlusion model, infarcts involved mainly the capudoputamen after 60 minutes of temporary occlusion but encompassed the whole caudoputamen and large parts of the neocortex, resembling the lesions observed with permanent occlusion, after 180 minutes of occlusion. Based on these observations and our data, it appears that in rat temporary MCA occlusion models, 1 hour of ischemia is reproducibly associated with ischemic lesion reversibility, particularly in neocortical regions.

In similar rat suture MCA occlusion models, blood flow in the MCA territory drops to 2–30% of baseline levels during arterial occlusion but recovers to approximately 70% 2 hours after withdrawal of the occluder. We performed the perfusion MRI studies to qualitatively document lack of tissue perfusion during arterial occlusion and restoration of tissue perfusion after withdrawing the occluder because this method was readily adaptable to the present study, which used rats not subjected to craniectomy, examined in a strong magnetic field, and permitted to survive for 24 hours. A recent study confirmed the reliability of the perfusion MRI technique for detecting ischemic regions. The significant correlation of perfusion scale grade with DWI %HLA during ischemia in the present study supports this observation. The perfusion MRI studies qualitatively demonstrated recovery of perfusion after withdrawal of the occluder but did not always show normal perfusion, probably related to perfusion disturbances during recirculation previously observed after global and focal brain ischemia in animals.

DWI offers a novel method for rapidly identifying regions of ischemic injury in vivo and could potentially help to determine which tissue damage is reversible. Warach et al have demonstrated that DWI can show an infarct during the first few hours after stroke onset in humans, in agreement with previous animal studies. This method might be adaptable to treatment trials of human stroke because it offers the capability to monitor the evolution of ischemic tissue damage, as shown in the present study. Further investigations are necessary to obtain more accurate indicators for tissue damage reversibility in ischemic regions and to apply this technology as an in vivo assessment of therapeutic intervention for animal and human ischemic stroke.

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References

Water molecules in tissue undergo semirandom translational movement, known as restricted diffusion. The associated coefficient of diffusion is exquisitely sensitive to the viscosity of the tissue and the presence and integrity of cellular structures. With the imposition of pulsed magnetic field gradients onto spin/echo magnetic resonance imaging (MRI), 1 changes of restricted diffusion of water protons in intact and damaged tissues can be presented in an image format and highlighted.2 The technique of generating image contrast based on differences of restricted diffusion coefficients of water protons in tissue is known as diffusion-weighted MRI (DWI).3

In a major step forward in the application of DWI to the investigation of cerebral ischemia, Minematsu et al report that DWI performed within 30 minutes after transient occlusion of the middle cerebral artery in rats accurately predicts tissue destined for infarction and may discriminate between reversibly and irreversibly damaged tissue. DWI is emerging as an effective and sensitive imaging modality for studies of experimental cerebral ischemia. DWI allows recognition of focal ischemic tissue in rats in which recirculation can be introduced in the ischemic area.4

The evolution of the restricted diffusion coefficient in the lesion, and thereby the progression of ischemic cell damage, can be monitored,5 and in combination with T2-weighted imaging DWI may discern the pathophysiology of developing lesions.6 Movement of water is essential to cell viability, and alterations

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**Editorial Comment**

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