Relationship Between Magnetic Resonance Arterial Patency and Perfusion-Diffusion Mismatch in Acute Ischemic Stroke and Its Potential Clinical Use

Irina A. Staroselskaya, MD; Claudia Chaves, MD; Brian Silver, MD; Italo Linfante, MD; Robert R. Edelman, MD; Louis Caplan, MD; Steven Warach, MD, PhD; Alison E. Baird, FRACP, PhD

Background: In patients with acute ischemic stroke the magnetic resonance (MR) perfusion-diffusion mismatch pattern (perfusion lesion at least 20% larger than the lesion on diffusion-weighted imaging) may indicate ischemically threatened but viable tissue. To our knowledge, the relationship of this MR pattern to serial changes in MR angiography (MRA) has not been reported.

Objectives: To investigate the relationship between MRA changes and patterns of diffusion-weighted imaging and perfusion abnormalities and to determine if the information obtained could be used in clinical management.

Methods: The MR studies of 35 patients who had undergone sequential multimodality MR imaging studies within the first 4 days of stroke were reviewed. All lesions were in the internal carotid artery territory distribution. Magnetic resonance angiographies were read by 2 observers blinded to the clinical data.

Results: During the first 24 hours a perfusion-diffusion mismatch was present in 22 (92%) of the 24 patients with an MRA arterial occlusive lesion. (At this time 5 [46%] of the 11 patients with a normal MRA [P = .006] also had a mismatch.) Two to 4 days after stroke, of these 22 patients resolution of the mismatch occurred in 8 (87%) of 9 patients with recanalization on MRA compared with 5 (39%) of 13 patients without arterial recanalization (P = .03). Resolution of mismatch occurred in 3 (60%) of 5 patients with a normal MRA and a mismatch at the first time point.

Conclusions: Concordance between MRA and the MR perfusion-diffusion mismatch pattern provides supportive evidence for an arterial vascular basis for this MR signature in acute stroke. Discordance between MRA lesions and mismatch may result from arterial branch occlusions undetected by MRA or from an alternate mechanism for the mismatch. The MR imaging patterns identified extend our understanding of the pathophysiology of stroke and may contribute to the improvement of stroke management in the future.

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OVER THE PAST decade new magnetic resonance imaging (MRI) techniques have become available providing new opportunities for the investigation of stroke. These include diffusion-weighted imaging (DWI), which provides a measure of cellular injury and cytotoxic edema, MR perfusion imaging, and MR angiography (MRA). Application of these methods might identify particular pathophysiological patterns and stroke subtypes against which more specific therapies could be targeted.1-2

In previous MRI studies it has been shown that tissue at risk for enlargement of the ischemic lesion may exist when the area of ischemic injury on DWI is surrounded by a larger area of hypoperfusion as measured by the mean transit time map.3-10 Since this pattern of tissue abnormalities may indicate ischemic, but potentially salvageable, tissue, it could form a template for therapeutic trials.2,8,11 However, not all of the DWI lesion may be irreversibly injured and not all of the hypoperfused tissue may be at risk.

The clinical and angiographic correlates of changes in MR perfusion and diffusion lesions have not been clearly defined or the optimal usage determined. We hypothesized that during the first 24 hours of stroke an arterial lesion seen on MRA would commonly be associated with a perfusion-diffusion mismatch, while patients with a normal MRA would not have a mismatch. We also hypothesized that reopening of the artery on MRA at 2 to 4 days would more commonly correlate with resolution of the perfusion-diffusion mismatch.
PATIENTS AND METHODS

PATIENTS

All eligible patients in the Stroke MRI database (1993-1999) at the Beth Israel Deaconess Medical Center, Boston, Mass, were identified and included in the study. Inclusion criteria for the study were that (1) patients had undergone 2 MRI studies during the acute phase of stroke, the first one during the first 24 hours and the second at 2 to 4 days, and (2) the lesions were in the distribution of the internal carotid artery territory. Patients with lacunar stroke were excluded from this study. The time from the onset of stroke was backdated to when the patient was last known to have no neurologic deficit. Enrollment in other trials of new therapies did not exclude patients from inclusion in this study. Three patients had received recombinant tissue plasminogen activator therapy.

MAGNETIC RESONANCE IMAGING

Magnetic resonance DWI was obtained using the methods described in our previous articles.œAll studies were performed using a 1.5-T MR whole-body system (Siemens AG, Erlangen, Germany), the Vision system or its prototype. Diffusion-weighted imaging used multislice, single-shot, echo-planar imaging with b values between 0 and 1000 s/mm². Perfusion imaging used a dynamic first pass bolus tracking of gadolinium diethylene-triamine penta-acetic acid and a multislice gradient echo-planar sequence with the following parameters: echo time, 60 milliseconds; repetition time, 2 seconds; field of view, 260 cm; acquisition matrix, 128 × 128 pixels, and slice thickness, 7 mm with no gaps. Twelve slices were acquired at exactly the same position as on DWI. Head and neck MRAs were performed for all patients. Intracranial MRA used a rapid (2 minutes 39 seconds) 3-dimensional time of flight technique obtained in the region of the circle of Willis and was performed at the same time as DWI. A flow-compensated gradient-echo sequence was used with imaging parameters of 40/7 milliseconds (ie, repetition time, 40 milliseconds; echo time, 7 milliseconds); flip angle, 20°; slab thickness, 40 to 50 mm; acquisition matrix, 256 × 256 pixels; and field of view, 21 cm. Neck MRAs were performed within 24 hours of DWI.

DATA ANALYSES

The dynamic perfusion series was processed on a pixel-by-pixel basis to produce a variety of maps related to cerebral blood volume and tissue perfusion. The relative mean transit time map was calculated from the first moment to the peak in the deltaR2* fitted curves.œIt was found that this image provided the most distinct perfusion defect border as previously described,œas well as providing the maximum anatomical extent of the perfusion abnormality.œFor data analyses the volumes of the DWI and relative mean transit time map lesions were used. The lesion volumes had been measured twice by observers (I.A.S. and A.E.B.) blinded to the clinical data, with an interobserver reliability of r>0.95. The accuracy of volumetric measurements at our center has been validated in a phantom stroke model described by Laubach et al.œ

The MRAs were read by 2 observers (I.A.S. and A.E.B.) blinded to the clinical data. All MRA lesions were identified as occlusive or stenotic. If there was an initial disagreement, a final decision was reached by consensus. The following definitions were used. An abnormality on MRA, whether stenotic or occlusive, was denoted an arterial lesion. A perfusion-diffusion mismatch was defined as a perfusion lesion (as measured on the relative mean transit time map) at least 20% larger than the DWI lesion volume. The 20% value was a conservative measure chosen to allow for error in volumetric measurements. The size of the mismatch was further quantitated by the following calculations. The relative mismatch size was defined as: [(perfusion lesion volume – DWI lesion volume)/perfusion lesion volume] The absolute mismatch size was calculated: perfusion lesion volume – DWI lesion volume.

STATISTICAL ANALYSES

χ² Statistics, Fisher exact tests, Mann Whitney tests, and 1-way analyses of variance were used for statistical analyses. A 1-sided Fisher exact test was used when the expected cell counts in one of the cells was below 5. P<.05 was considered statistically significant. All values are expressed as means (±SDs).

RESULTS

Thirty-five patients fulfilled the inclusion criteria. There were 22 men and 13 women. The mean age was 67.7 ± 18.3 years (age range, 22-90 years). The mean time of the first MR study was 8.0 ± 4.8 hours (range, 2-22 hours).

FIRST 24 HOURS

In the first 24 hours MRA arterial lesions were present in 24 (69%) of the 35 patients while no lesion was identified in the other 11 patients (31%) (Table 1). No significant difference was noted in the time of MR study between the 2 groups. Arterial lesions were present in the middle cerebral artery in 14 patients, involving the M1 segment in 10 (bilateral in one patient, middle cerebral artery and anterior cerebral artery lesions in another patient), M2 segment in 2 patients, and M3 segment in 2 patients. There was 1 patient with a lesion in the anterior cerebral artery and 9 patients with lesions in the proximal internal carotid arteries (ICAs). Two patients had additional lesions in the arteries of the posterior circulation. The perfusion lesion volume was significantly larger in patients with an arterial lesion (P<.001, Mann Whitney test), the mean perfusion lesion size being 112.2 ± 75.6 mL in patients with an arterial lesion compared with 16.8 ± 25.7 mL in patients without a lesion. In 3 patients with normal MRAs, the perfusion lesion size was greater than 30 mL, larger than might be expected from an M3 arterial branch occlusion. Two had striatocapsular infarcts from presumed lenticulostriate arterial occlusion. The mean DWI lesion size was larger in patients with an arterial lesion (17.2 ± 21.7 mL) compared with 6.1 ± 5.3 mL in patients without an arte-
arterial occlusion, the DWI lesion expanded to become

At this time point (<24 hours after the onset of stroke) a perfusion-diffusion mismatch was present in 22 (92%) of the 24 patients with an arterial lesion on MRA compared with 5 (46%) of the 11 patients with a normal MRA (P = .006, χ² test; Table 1). All 9 patients with ICA lesions had a mismatch. The absolute and relative mismatch sizes were significantly smaller in patients with a normal MRA than in patients with an abnormal MRA. The mean absolute mismatch size was 122.4 ± 70.4 mL for patients with an arterial lesion compared with 33.6 ± 31.5 mL (P = .02, Mann-Whitney test) in those without. The mean absolute mismatch size was 103.9 ± 75.6 mL for patients with an arterial lesion compared with 26.2 ± 32.6 mL (P = .02, Mann-Whitney test) in those without. The mean relative mismatch size for patients with an ICA lesion was 128.9 ± 76.8.

FOLLOW-UP STUDY 2 TO 4 DAYS AFTER STROKE

By 2 to 4 days, partial or total recanalization had occurred in 9 (38%) of the 24 patients with an arterial lesion at the first time point (Table 2). Only 1 of the 9 patients with ICA lesions showed recanalization while 8 of the 14 patients with middle cerebral artery lesions showed recanalization. One patient with an anterior cerebral artery lesion did not show recanalization—a stenotic lesion at the first time point became completely occluded at the second time point. Four of the 10 patients with M1 middle cerebral artery lesions showed recanalization while all 4 patients with M2 and M3 lesions showed recanalization. The MRAs were unchanged in the 11 patients with a normal MRA at the first time point.

Of the 22 patients with an arterial lesion and a mismatch at the first time point, by 2 to 4 days the perfusion-diffusion mismatch resolved in 8 of the 9 patients with arterial recanalization, compared with 5 of the 13 patients without recanalization on MRA. Three of the 5 patients with a normal MRA and mismatch at the first time point showed resolution of the mismatch at the second time point. The size of persisting mismatches was largest in patients without arterial recanalization.

The mean mismatch sizes at this time point are given in Table 2. In the one patient with recanalization and persisting mismatch, the relative mismatch size was 47.7 compared with 110.9 ± 76.2 mL for patients without recanalization and those with a normal MRA. The results are further illustrated in Figure 1, with images from representative cases shown in Figure 2.

On the follow-up study DWI lesion evolution (enlargement by at least 20%) had occurred in 20 of the 24 patients with an arterial lesion at the first time point compared with 8 of the 11 patients (P > .05) with a normal MRA. The mean absolute difference in the DWI lesion volume was 16.0 ± 28.3 mL compared with 1.7 ± 4.87 mL, respectively (P = .01). There was insufficient data at the chronic time points to study the effect on final infarct volume.

In this study, the serial changes in arterial lesions and their relation to perfusion-diffusion mismatch as measured by multimodality MRI were examined. The results of this investigation partially confirmed our initial hypotheses. The frequent finding of a perfusion-diffusion mismatch with an arterial lesion (92%) suggested an arterial vascular ba-

### Table 1. Relationship Between Mismatch and Arterial Lesions in the First 24 Hours of Ischemic Stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>Abnormal MRA (n = 24)</th>
<th>Normal MRA (n = 11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion Volumes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perfusion, mL</td>
<td>112.2 ± 75.6</td>
<td>16.8 ± 25.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>DWI, mL</td>
<td>17.2 ± 21.7</td>
<td>6.1 ± 5.3</td>
<td>.45</td>
</tr>
<tr>
<td>Mismatch</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present, No. (%) of patients</td>
<td>22 (92)</td>
<td>5 (46)</td>
<td>.006</td>
</tr>
<tr>
<td>Absolute size, mL</td>
<td>103.9 ± 75.6</td>
<td>26.2 ± 32.6</td>
<td>.02</td>
</tr>
<tr>
<td>Relative size</td>
<td>122.4 ± 70.4</td>
<td>33.6 ± 31.5</td>
<td>&lt;.005</td>
</tr>
</tbody>
</table>

*Relationship between arterial patency and perfusion and diffusion-weighted imaging (DWI) lesions in the first 24 hours of stroke. The perfusion lesion volumes were significantly larger in patients with an arterial occlusion. A perfusion-diffusion mismatch was found in 22 of the 24 patients with an arterial occlusion compared with 5 of the 11 patients with a normal magnetic resonance angiogram (MRA). All data are given as mean ± SD unless otherwise stated.

### Table 2. Relationship Between Mismatch and Arterial Recanalization at 2 to 4 Days

<table>
<thead>
<tr>
<th>First 24 Hours</th>
<th>Abnormal MRA</th>
<th>Normal MRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>24</td>
<td>11</td>
</tr>
<tr>
<td>No. of mismatches</td>
<td>22</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2-4 Days</th>
<th>No Recanalization</th>
<th>Recanalization</th>
<th>Normal MRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>9</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Mismatch</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute size, mean ± SD, mL</td>
<td>47.7</td>
<td>110.9 ± 76.2</td>
<td>43.05 ± 32.2</td>
</tr>
<tr>
<td>Relative size, mean ± SD</td>
<td>23.7</td>
<td>9.9 ± 10.5</td>
<td>23.3 ± 23.2</td>
</tr>
</tbody>
</table>

*On the follow-up magnetic resonance imaging study at 2 to 4 days, of 24 patients with an abnormal magnetic resonance angiogram (MRA) at the first time point showed recanalization. Of the 22 patients with an arterial lesion and a mismatch at the first time point, by 2 to 4 days the perfusion-diffusion mismatch resolved in 8 of the 9 patients with arterial recanalization, compared with 5 of the 13 patients without recanalization on MRA. Three of the 5 patients with a normal MRA and mismatch at the first time point showed resolution of the mismatch at the second time point. The size of persisting mismatches was largest in patients without arterial recanalization.

COMMENT
MRA and a perfusion-diffusion mismatch at the first time point can be made. First, in the 5 patients with a normal perfusion and DWI were not entirely concordant. In patients in whom the arterial lesion persisted but in whom the mismatch resolved at the second time point, we suggest that (1) recruitment of the collateral circulation could have led to restored tissue perfusion, (2) the DWI lesion could have expanded to its maximal size so that the DWI and perfusion lesions became congruent, or (3) there was clearing of a distal tandem arterial lesion.

There have been several preliminary reports of the correlation between MRA and perfusion and diffusion lesions at one time point during the first 24 to 48 hours of ischemic stroke. Barber et al also found that a mismatch was more likely to be present and of larger size in patients with an arterial lesion on MRA: further, on review of their data 5 of 17 patients with a mismatch had a normal MRA in the first 24 hours of stroke. Conversely, Rordorf et al did not find a significant mismatch in any of their patients with normal MRA although the use of relative cerebral blood volumes may explain this finding. In the early study of Warach et al relative cerebral blood volumes abnormalities were found in 15 of 16 patients with arterial lesions on MRA. Neumann-Haefelin and colleagues also reported that patients with ICA lesions had the largest mismatches of all. In patients undergoing thrombolysis, Schellinger et al reported more extensive tissue reperfusion and arterial recanalization with recombinant tissue plasminogen activator therapy, with subsequently smaller infarct size.

In looking at the cases with discordance between MRA and the perfusion-diffusion mismatch, a few speculations can be made. First, in the 5 patients with a normal MRA and a perfusion-diffusion mismatch at the first time point, it seems likely that there may have been an arterial lesion below the resolution of the MRA as mentioned earlier. The finding of smaller perfusion lesions in patients with a normal MRA provides support for this theory. However, local or alternate mechanisms of tissue ischemia should not be disregarded. Cerebral arterial occlusions cannot be detected short-term in up to 20% to 30% of stroke patients even using conventional angiography, in up to 30% of patients the stroke mechanism cannot be determined. Perhaps in a few cases this pattern could be analogous to syndrome X in the cardiac literature—ischemia in the presence of normal coronary arteries—that may be attributed to microvascular disease. Alternatively, in some of these 5 patients and the 1 patient where the MRA showed recanalization but the mismatch remained, there may have been a no-reflow phenomenon after recanalization. Conventional angiographic studies or higher resolution MRA that may provide better arterial definition and MRI studies conducted earlier after stroke onset might have a greater probability of detecting arterial occlusive lesions. A comparison of the evolution of the DWI lesions between patients with and without arterial lesions at the first time point could provide further insights. In our study, most patients showed DWI lesion enlargement at 2 to 4 days, but this is a time when DWI lesions are confounded by edema.

Second, in patients in whom the arterial lesion persisted but in whom the mismatch resolved at the second time point, we suggest that (1) recruitment of the collateral circulation could have led to restored tissue perfusion, (2) the DWI lesion could have expanded to its maximal size so that the DWI and perfusion lesions became congruent, or (3) there was clearing of a distal tandem arterial lesion.

Figure 1. A, In the first 24 hours magnetic resonance angiography (MRA) arterial lesions were present in 24 (69%) of the 35 patients. In the other 11 patients (31%) the MRA was normal. By 2 to 4 days, partial or total recanalization had occurred in 9 (38%) of the 24 patients with an arterial lesion at the first time point. The MRAs were unchanged in the 11 patients with normal MRA at the first time point. B, At the first time point (<24 hours after the onset of stroke) a perfusion-diffusion mismatch was present in 22 (92%) of the 24 patients with an arterial lesion on MRA compared with 5 (46%) of the 11 patients with a normal MRA (P = .006, x² test). By the time of the follow-up study 1 (13%) of the 9 patients with arterial recanalization had a persistent perfusion-diffusion mismatch compared with 8 (57%) of the 15 patients without persistent arterial lesion (P = .05, Fisher exact test). In 2 patients with persisting arterial lesions, the diffusion-weighted imaging lesion had evolved to become equivalent to the perfusion lesion volume. A perfusion-diffusion mismatch was present in 2 (18%) of the 11 patients with normal MRA at the follow-up time point compared with 5 of the 11 patients at the time of the first study. In 2 cases the perfusion lesion had resolved and in 1 the DWI lesion had evolved to become equivalent to the perfusion lesion volume.
reports from angiographic studies in the 1980s. Further, the pattern of arterial recanalization and the recanalization rate on MRA of 38% by 2 to 4 days were similar to prior angiographic reports. We acknowledge that it is possible that in some patients at the first time point, when an arterial lesion was seen, there was already partial recanalization. Similarly, we acknowledge that the optimal MR perfusion map for use in these studies is a matter of current debate and that the relative mean transit time map may overestimate the volume of the perfusion abnormality and the tissue at risk.

The results raise the question: which is the best MRI template in the thrombolysis setting—an MRA-identified lesion or the perfusion-diffusion mismatch? Most prior MRI studies have proposed that only patients with a mismatch should receive thrombolytic therapy because they are the individuals with potentially salvageable tissue via reperfusion thereby minimizing the risk to other patients. However, this proposal has been controversial becauseage of uncertainty over the exact pathophysiological basis of the mismatch and because of variable clinical correlations of lesion volumes. Whether DWI lesion evolution always represents recruitment of the penumbra, or other processes such as delayed neuronal injury and apoptosis, is still to be determined.

The one currently approved therapy for stroke—recombinant tissue plasminogen activator administered intravenously within 3 hours—is believed to work by opening large cerebral arteries occluded by thromboembolic material. Therefore, it seems reasonable that arterial imaging should be a best start to guide therapy (whether by MRA, transcranial Doppler ultrasound, or by angiography). We propose that the optimal candidate for thrombolysis is the patient with a documented arterial occlusion and a mismatch. The Prolyse in Acute Cerebral Thromboembolism II study has shown that when
patients are highly selected on the basis of their arterial lesion (M1 and M2 occlusions only), reperfusion can be effectively carried out up to 6 hours after stroke.28

The optimal treatment of patients with a mismatch and normal MRA is one of speculation. Some patients may have an arterial occlusion below the resolution of the MRA. The prevailing thinking is that these may be amenable to recanalization with tissue plasminogen activator therapy, although it is acknowledged that these branch occlusions have a high and early rate of spontaneous recanalization. In other cases, however, there may be altered tissue perfusion and microcirculation as the basis for this change.29 Perhaps this group of patients might specifically benefit from reperfusion therapies that might work on the microcirculation,26,28,30

Evaluating the mismatch with the MRA gives the following 4 ischemic stroke patterns: abnormal MRA, mismatch; abnormal MRA, no mismatch; normal MRA, mismatch; and normal MRA, no mismatch. These patterns may provide a more rational approach to treatment.

Concordance was frequently found between changes in the putated tissue at risk (the mismatch) and changes in arterial patency as measured by MRA. Discordance between MRA lesions and mismatch may have resulted from arterial branch occlusions undetected by MRA or from an alternate mechanism for the mismatch. The 4 MRI patterns identified could provide a pathophysiological basis that, in combination with clinical features, could lead to a more rational approach to the management of stroke patients and the design of stroke trials.

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Corresponding author: Alison E. Baird, FRACP, PhD, National Institute of Neurological Disorders and Stroke, National Institutes of Health, 36 Convent Dr, MSC 4129, Room 4A03, Bethesda, MD 20892-4129 (e-mail: bairda@ninds.nih.gov).

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