Time Course of Lesion Development in Patients With Acute Stroke
Serial Diffusion- and Hemodynamic-Weighted Magnetic Resonance Imaging

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Background and Purpose—We sought to characterize the evolution of acute ischemic stroke by MRI and its relationship to patients’ neurological outcome.

Methods—Fourteen patients with acute ischemic stroke underwent MRI within 13 hours of symptom onset (mean, 7.4 ± 3 hours) and underwent repeated imaging and concurrent neurological examination at 8, 24, 36, and 48 hours and 7 days and >42 days after first imaging.

Results—Diffusion-weighted imaging (DWI) lesion volumes increased between the first and second scans in 10 of 14 patients; scans with maximum DWI lesion volume occurred at a mean of 70.4 hours. Initial DWI lesion volume correlated with the largest T2 lesion volume ($r = 0.97; P < 0.001$). Final lesion volume was smaller than maximum lesion volume in 12 of 14 patients. There was positive correlation between the follow-up National Institutes of Health Stroke Scale score and the initial DWI lesion volume ($r = 0.67; P = 0.01$) and maximum T2 lesion volume ($r = 0.77; P < 0.01$) and negative correlation with initial mean apparent diffusion coefficient ratio (ADCr) ($r = -0.64; P < 0.05$). The ADCr was 0.73 at initial imaging and fell between the initial and second scans in 10 of 14 patients. Mean ADCr did not rise above normal until 42 days after stroke onset ($P < 0.001$).

Conclusions—Serial MRI demonstrates the dynamic nature of progressive ischemic injury in acute stroke patients developing over hours to days, and it suggests that both primary and secondary pathophysiological processes can be valuable targets for neuroprotective interventions. (Stroke. 1998;29:2268-2276.)

Key Words: diffusion ■ magnetic resonance imaging ■ perfusion ■ stroke, acute

Acute ischemic stroke is a major cause of death and disability in humans, and many strategies for acute neuroprotection in this setting are being evaluated.1 Recently, reperfusion with intravenous recombinant tissue plasminogen activator was shown effective in a double-blind, placebo-controlled randomized clinical trial of acute ischemic stroke in humans.2 Data from animal stroke models and clinical trials suggest that intravenous thrombolytic therapy must be initiated at a very early stage of infarct evolution.3,4 Without a means to identify pathological stages of ischemic injury, time from onset of symptoms is now used to guide therapy. The temporal evolution of acute ischemic brain pathology in humans is variable, depending on a variety of other factors, including the underlying vascular lesion. Positron emission tomography (PET) studies in human stroke have identified areas of “tissue at risk,” and MR-based studies have demonstrated growth of cerebral infarction over time.5–7 Novel MRI techniques that identify cerebral ischemic injury, eg, diffusion-weighted imaging (DWI), and perturbations in cerebral perfusion, eg, hemodynamic-weighted imaging (HWI), offer the ability to identify early progression of ischemic injury and tissue at risk both in animal experiments and in the emergency evaluation of patients.8–13

In experimental animal models, decreases in the apparent diffusion coefficient (ADC) of water produce increased signal intensity on DWI within minutes of focal cerebral ischemia.4 Pooled data from multiple subjects scanned at various times after stroke onset or from individual patients studied at 2 time points suggest that ADC, DWI, and T2 can define a temporal evolution of MR tissue characteristics in the early stages of cerebral infarction.14–17 With the addition of HWI, MRI can also identify an even earlier stage of ischemia in regions of brain with abnormal blood volume but normal ADC and DWI.18 The goal of this study is to demonstrate the evolution of cerebral infarc-
tion with repeated DWI and HWI in individual patients and to correlate these findings with clinical outcome.

Subjects and Methods
Fourteen patients were enrolled into the study. Inclusion criteria included the following: (1) Subjects had well-defined onset of an acute stroke syndrome. (2) Acute stroke protocol MRI was performed within 13 hours of stroke onset with a lesion visible on DWI. (3) Subjects were ineligible for thrombolytic therapy or an investigational neuroprotective drug. (4) Subjects were capable of tolerating repeated MRI without need for sedation. (5) Informed consent was obtained from the patient or family member. All patients meeting criteria were enrolled consecutively in the study by a member of the Acute Stroke Service at our institution. Suitability to undergo multiple scans in the first 48 hours may have skewed the study population to those with mild to moderate deficits. In no case was a patient screened and the initial DWI scan normal. National Institutes of Health Stroke Scale scores (NIHSSS) were recorded at the time of each scan, and subjects were measured with the Barthel Index after a minimum follow-up of 6 weeks. All strokes were classified by vascular territory and stroke mechanism according to the Trial of Org 10172 in Acute Ischemic Stroke (TOAST) study criteria. The study was approved by the Subcommittee on Human Studies at our institution. Use of heparin, warfarin, aspirin, antihypertensives, or vasopressors varied according to clinical circumstances. All patients were imaged within 13 hours of the onset of ischemic symptoms. One patient (patient 3) was transferred to another hospital after 24 hours and died before long-term follow-up because of a malignancy. Patients received up to 6 follow-up scans at defined intervals after enrollment: 8 ± 2 hours, 24 ± 4 hours, 36 ± 4 hours, 48 ± 4 hours, hospital day 7 or discharge, and final follow-up at ≥ 6 weeks. Scans were postponed or canceled if the patient’s medical condition became too unstable or at the family’s request.

Imaging Parameters
The image sequences required 35 minutes to be performed on our inpatient MRI scanner at 1.5 T (Signa; GE Medical Systems) with an echo-planar readout (Advanced NMR Systems, Inc.) and included sagittal T1, axial DWI, echo-planar imaging T2, proton density, HWI, postgadolinium axial T1, and 2-dimensional phase-contrast MR angiography of the circle of Willis. The DWI and HWI images were performed with a 40 × 20-cm field of view and 256 × 128-pixel matrix, MR angiography with a 24 × 18-cm field of view and 256 × 128-pixel matrix, and all others with a 20 × 20-cm field of view and 256 × 192-pixel matrix. DWI and low-b-value T2 images were obtained with b values of 1221 and 3 s/mm², respectively. To avoid errors due to white matter anisotropy, the diffusion tensor trace was repeatedly sampled along the orthogonal planes to produce trace ADC maps. Isotropic DWI and low-b-value images were available for clinical interpretation. HWI was performed during rapid injection through an 18-gauge antecubital catheter of 0.2 millimoles per kilogram of gadodiamide or gadopentetate dimeglumine with the use of dynamic susceptibility imaging techniques. These images were processed off-line to create maps of relative cerebral blood volume (CBV). A more detailed description of our DWI and HWI MR protocol has been previously reported.

Statistical Analysis
The areas of signal hyperintensity on high-b-value axial DWI and coregistered low-b-value axial T2 images were identified with a semiautomated segmentation algorithm in a commercial imaging software package (Alice, Hayden Imaging Processing Group). These images were then manually edited to conform to anatomic boundaries by a trained research assistant (B.W.) blinded to the clinical history. Regions of interest were reviewed and approved by an experienced neuroradiologist (R.B.) and 2 stroke neurologists (L.H.S., W.J.K.). The regions of interest, which were composed of the entire region of DWI hyperintensity, were then copied and projected onto the ADC maps in both the abnormal and corresponding contralateral normal brain parenchyma. Further manual editing of the region of interest overlay was performed in the contralateral hemisphere to ensure appropriate anatomic symmetry. The ADC measurements reported in this study are the mean relative ADC values for the entire lesion volume (as identified on the DWI images). Lesion volumes were calculated as the sum of each slice area multiplied by the slice thickness. All image analysis was performed on a PowerMac platform from images windowed for optimal contrast that had not undergone any postprocessing.

To control for differences in absolute ADC values at any given scan (e.g., brain temperature, ion concentrations) and to permit more meaningful and reliable comparisons between initial and subsequent scans among individuals and across groups, an ADC ratio (ADCr) was calculated. ADCr was calculated by dividing the mean ADC of the stroke lesion volume by the mean ADC of the normal contralateral mirror image region (ADCr = Stroke ADC/Contralesional). Regional decreases in CBV were determined by an analogous technique of outlining regions of decreased signal intensity on the CBV images. Reperfusion was defined as an improvement of ≥ 60% from the initial volume of decreased CBV intensity. Hyperemia was defined as a region of increased CBV intensity and was not included in the calculated CBV deficits.

Comparisons of ADCr between patients and across time epochs were analyzed with 2-tailed Student’s t test (null hypothesis, ADCr = 1), and all correlation coefficients are expressed as pairwise Pearson’s product-moment r and P values. Analysis was performed within JMP and SAS statistical software (SAS Institute).

Results
Fourteen patients received a total of 86 MR scans, and 93% (13/14) received 3 MRI scans within the first 36 hours after stroke onset. Mean duration between stroke symptom onset and first MR scan was 7.4 hours (range, 1.6 to 13 hours). An MRI scan after 5 days was obtained in 71% (10/14), and 43% (6/14) had a repeated MRI between 6 and 10 days after stroke onset. Mean duration of final follow-up MR scan was 138 ± 91 days (range, 43 to 333 days). The Table summarizes the demographic and clinical data. The study included 5 women and 9 men (mean age, 58 years). The mean NIHSS on admission was 6.5. Eight patients were diagnosed with embolic strokes (5 in middle cerebral artery [MCA] territory, group A; 1 in anterior cerebral artery territory and 2 in the posterior circulation, group B). Six were diagnosed with anterior circulation small-vessel occlusive strokes.

ADC Change
The mean ADCr of the lesion on the initial scan was 0.73 (range, 0.54 to 0.91). The mean time to minimum ADCr was 32.7 hours (range, 6 to 61 hours). Figure 1 shows the histogram distribution of individual times to minimum ADCr; Figure 2 shows the ADCr at each time point for the individual patients. ADCr versus time data were analyzed by 2 methods. Data for the 13 of 14 patients in whom DWI and low-b-value T2 abnormalities were clearly and consistently visualized were grouped into the shortest time epochs that included only 1 data point per patient in each time epoch. Mean ADCr by time epoch decreased to a minimum of 0.65 at the 2- to 5-day epoch and did not statistically exceed 1 until 42 days after stroke onset (P < 0.01). Additionally, individual ADCr values were interpolated for 22 uniform time points after stroke onset according to a best-fit curve for each patient data plot. In this model, ADCr became > 1.0 at 28 days, but statistical significance for ADCr > 1 was not achieved until 49 days.
Interestingly, the initial ADCr was negatively correlated with the final NIHSSS at follow-up ($r = -0.64; P < 0.05$).

Lesion Volume Change

Increase from the initial DWI lesion volume on ≥1 subsequent scan was seen in 13 of 14 cases (all except patient 7; see below) and reached its maximum in the 14 cases at a mean of 70.4 hours (range, 13 to 247 hours) (Figure 1). Figure 3 shows a case of lesion volume growth in the acute stages by serial DWI scans. T2 lesion volume is the accepted MR measure of tissue infarction, and Figure 4 shows the initial DWI lesion volume expressed as a percentage of the largest lesion volume on T2 imaging for each patient. In 11 of 14 cases, the initial lesion volume on DWI was less than the largest T2 lesion volume (mean, 64 $\pm$ 23%; range, 23% to 95%). In the other 3 cases, the first (patient 3) withdrew from the study at 24 hours, likely before maximum T2 lesion volume was attained. In the second (patient 10), the original ocipital hyperintensity was obscured on the scan at 5 to 20 days but reappeared on the final image at 278 days associated with tissue loss. There was evidence of hemorrhagic transformation, which may have attenuated or “fogged out” the T2 signal on the scan at 5 to 20 days and likely led to an underestimation of the maximal T2 infarct volume. The third (patient 9) had a tiny small-vessel occlusive stroke better visualized on DWI than on T2 images because of the increased conspicuity on DWI.

In all cases in this series, the regions initially abnormal on DWI developed hyperintensity on T2 imaging consistent with infarction. Lesion growth occurred as a result of expansion of the initial lesion or the appearance of small regions of infarction within the same vascular territory. In no case in this series did a new lesion in a second vascular territory occur. Figure 5 shows the absolute (not relative) lesion volumes and the correlations between largest T2 lesion volume and the initial DWI ($r = 0.97, P < 0.001$) and between largest T2 lesion volume and initial CBV lesion volumes ($r = 0.67, P < 0.05$).

Growth of the stroke lesion volume on DWI over time is shown for each case in Figure 6. Several features of lesion growth are identified. First, sustained lesion growth (over 1 to 2 days) was observed in 10 patients (patients 1, 2, 3, 4, 5, 6, 8, 11, 13, and 14) from the initial to the second and from the second to the third or fourth scan. Second, over the subacute phase there were 2 patterns of lesion volume change. In 8 cases (patients 2, 5, 6, 7, 11, 12, 13, and 14) a plateau in stroke size was seen during the period 2 to 3 days after stroke onset, and in 3 cases (patients 1, 4, and 9) lesion volume peaked and then declined by imaging at 6 to 14 days. When all available cases were examined, the lesion volume on initial DWI was always smaller than the T2 lesion volume on the 6- to 10-day scan (n=6; mean initial DWI/6- to 10-day T2

### Table: Patient Demographics, Stroke Type, and NIHSSS Over Time

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Age/ Sex</th>
<th>Vascular Territory</th>
<th>Stroke Type</th>
<th>Time After Stroke</th>
<th>Initial Scan</th>
<th>NIHSSS at Time of Scan Interval</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>65/F</td>
<td>ACA</td>
<td>IS-cu</td>
<td>7</td>
<td>0</td>
<td>+8 h 1 2 4 3 2 0 0 0</td>
</tr>
<tr>
<td>2</td>
<td>43/F</td>
<td>Ant-chr</td>
<td>SV0</td>
<td>7</td>
<td>0</td>
<td>+24 h 1 2 3 2 0 0 0</td>
</tr>
<tr>
<td>3</td>
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<td>MCA</td>
<td>SV0</td>
<td>10</td>
<td>16</td>
<td>+36 h * * * * *</td>
</tr>
<tr>
<td>4</td>
<td>34/M</td>
<td>MCA</td>
<td>IS-om</td>
<td>4</td>
<td>17</td>
<td>+48 h * * * * *</td>
</tr>
<tr>
<td>5</td>
<td>79/M</td>
<td>SCA</td>
<td>IS-cu</td>
<td>6</td>
<td>3</td>
<td>+5–20 h * * *</td>
</tr>
<tr>
<td>6</td>
<td>58/F</td>
<td>MCA-sv</td>
<td>SV0</td>
<td>8</td>
<td>3</td>
<td>Final Scan</td>
</tr>
<tr>
<td>7</td>
<td>73/M</td>
<td>MCA</td>
<td>IS-cu</td>
<td>6</td>
<td>3</td>
<td>Final Scan</td>
</tr>
<tr>
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<td>IS-om</td>
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<td>12</td>
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<tr>
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<td>2</td>
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<tr>
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<td>IS-cu</td>
<td>11</td>
<td>2</td>
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<tr>
<td>11</td>
<td>31/M</td>
<td>MCA</td>
<td>IS-cu</td>
<td>6</td>
<td>17</td>
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<tr>
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<tr>
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<td>MCA</td>
<td>IS-om</td>
<td>10</td>
<td>14</td>
<td>Final Scan</td>
</tr>
</tbody>
</table>

ACA indicates anterior cerebral artery; Ant-chr, anterior choroidal artery; MCA-sv, middle cerebral artery small-vessel branch; SCA, superior cerebellar artery; PCA, posterior cerebral artery; IS-cu, ischemic stroke, cause unknown; SV0, small-vessel occlusion; and IS-om, ischemic stroke, other mechanism.

*N0 MR scan performed.

$\text{Figure 1.}$ Distribution of times to individual’s lowest ADCr value (mean, 32.7 hours) and times to individual’s maximum lesion volume measured on DWI (mean, 70.4 hours).
lesion volume = 60 ± 23%; range, 38% to 96%). Of importance for studies in which early and late lesion size comparisons were used, in 10 cases (patients 2, 4, 5, 7, 8, 9, 10, 11, 12, and 14) the lesion volume seen on the initial DWI and the maximum lesion volume ever seen on T2 were both greater than the T2 lesion on final follow-up.

The lesion volume was maximal on the initial DWI in only 1 patient (patient 7). In this case the initial scan was likely performed in the midst of reperfusion. This is suggested by the HWI, which showed increased CBV in some regions with visualized DWI hyperintensity (Figure 7). Complete reperfusion was seen on the repeated HWI 14 hours after stroke onset, and the lesion volumes on 5 scans over the next 5 days remained unchanged in this patient.

Half the cases (7/14) had evidence of abnormality on the initial low-b-value T2 images. In this study with mean time to initial scan of 7.5 hours, there was no significant difference in the interval from symptom onset to imaging in those with initial T2 hyperintensity (Figure 7). Complete reperfusion was seen on the repeated HWI 14 hours after stroke onset, and the lesion volumes on 5 scans over the next 5 days remained unchanged in this patient.

Figure 2. ADCr plotted against time from stroke onset in days for all cases. A, MCA embolic strokes; B, small-vessel strokes; and C, other embolic strokes. ADCr of 1 is highlighted by a black bar.

Significant reperfusion was defined as a reduction of the lesion on CBV map of >60%. Of the 5 patients with MCA territory stroke, 2 patients had early reperfusion (<15 hours), 2 had late reperfusion (>39 hours), and 1 had no reperfusion. Despite similar volumes on initial CBV abnormality, the 2 patients with early reperfusion had regions of increased CBV and clinical outcome by final NIHSSS (r = 0.66; P < 0.05). There was a trend toward significance in correlating T2 lesion volume with initial ADCr (r = −0.52; P = 0.06)

Hemodynamic-Weighted Imaging

The CBV images do not have the same degree of high signal-to-noise ratio as the DWI or ADC maps, and therefore we report only large changes in CBV apparent to visual inspection. In no case was there a major increase in the volume of CBV abnormality over time. In all but 3 patients (each with very small strokes) there was a detectable perfusion abnormality on HWI. In the 5 perforator cases with HWI, the initial lesion volume on HWI was less than on initial DWI. In 3 embolic strokes with HWI (2 MCA cases and 1 non-MCA), the initial lesion volume on HWI was greater than on initial DWI and on maximum T2.
intensity (probably due to hyperemia) and good outcomes with comparatively smaller final infarct volumes compared with those with late or no reperfusion (Figure 8).

For all patients regardless of stroke type, there was correlation between final clinical outcome (NIHSSS at follow-up) and the initial DWI lesion volumes ($r=0.67; P=0.01$) and maximum T2 ($r=0.77; P<0.01$). In group B patients with penetrator artery stroke, initial DWI correlated well with maximum T2 lesion volume ($r=0.97; P=0.01$) and initial CBV lesion volume ($r=0.95; P=0.01$). However, initial DWI did not correlate with severity of clinical deficits, which probably depends more on stroke location than size in small-vessel stroke. An area under the curve analysis was performed to determine whether changes in NIHSSS over time were significantly correlated with lesion volumes on T2, initial DWI, or initial CBV imaging, and no correlations were identified. For the 13 patients who completed the study to late follow-up (>42 days), there was the expected degree of clinical recovery with a reduction from a mean initial NIHSS score of 6.54 to a mean final NIHSS score of 2.08 ($P=0.01$). The mean Barthel Index at follow-up was 93.5 (range, 30 to 100).

**Discussion**

The hope for improved treatment for patients with acute stroke rests to a great extent on the ability to reverse the progressive changes that occur in ischemic human brain. DWI and HWI offer the potential to detect and measure some of these changes as they occur in patients or animal stroke models. The onset of brain ischemia is associated with a decrease in the mobility of water in affected brain tissue. This can be measured as a decrease in the ADC of water and contributes to the signal hyperintensity on DWI. This study provides the first published data on the temporal evolution of DWI lesion volume and ADC in individual patients with acute stroke.

Enlargement of stroke volume by DWI occurring over hours has been seen in multiple animal stroke studies. Data from these studies and a recent PET study in humans suggest that a goal of acute stroke therapy might be prevention of the enlargement of injured brain regions over time. In our initial report, we stated that 8 of 9 patients studied within 10 hours of stroke onset had growth of lesion volume by DWI into regions of CBV abnormality on the initial HWI. These data suggested that regions of abnormal perfusion (identified by HWI) might reflect penumbral tissue being recruited into infarction as the lesion volume (identified by DWI) expanded. Baird et al. studied 28 patients who were first scanned from 2 to 52 hours after stroke onset. They noted that enlargement in lesion volume was greatest in patients who were studied soon after stroke onset and that less growth was observed in patients who were first studied late after stroke.

![Figure 3](https://example.com/figure3.png)

**Figure 3.** Serial MRI of a patient (patient 11) with a left MCA stroke imaged at 6 hours after symptom onset. The arrows indicate a region of decreased relative CBV at 6 hours after stroke onset that is not fully reperfused 26 hours later and is associated with a lesion volume on DWI that increases 130% over the same time interval.

![Figure 4](https://example.com/figure4.png)

**Figure 4.** Lesion volume on the initial DWI scan expressed as a percentage of the largest lesion volume seen on T2-weighted imaging during the study.

![Figure 5](https://example.com/figure5.png)

**Figure 5.** Lesion volumes on the initial DWI and HWI scans plotted against the largest lesion volume seen on T2-weighted imaging during the study.
onset. Increase in lesion volume occurred in 70% of 13 patients in whom the initial perfusion abnormality was larger than the diffusion abnormality. Of interest, 24 of the scans showed a decrease in the size of the lesion over serial follow-up scans. It was suggested that this decrease in lesion volume was due to secondary processes such as confounding edema on the early scan or tissue atrophy on the late scan.

This series is the first to report multiple serial MR scans in individual stroke patients. All patients had an acute ischemic stroke and were scanned within 13 hours of stroke onset. The requirement that the patient consent to undergo multiple MRI scans during the study likely biased the population toward patients with less debilitating strokes (mean NIHSSS, 6.5) and smaller strokes (Figure 5). Despite this bias, a progressive increase in lesion volume in the first 24 hours after stroke occurred in 10 of 14 patients (Figure 6), suggesting expansion of the primary ischemic injury. Given the National Institute of Neurological Disorders and Stroke report of intravenous recombinant tissue plasminogen activator treatment improving outcome in patients with clinically diagnosed “small-vessel stroke,” it is of interest that an early increase in lesion volume was seen in 4 of 6 patients with deep penetrator artery strokes.

This serial study supplies unique information about the patterns of growth of lesion size. In all but 1 patient in this study, lesion volume on the final scan was appreciably lower than the maximum lesion seen during the acute hospital phase. In studies comparing early and late scans, Baird et al reported that the final lesion volume was frequently smaller than the initial. Given the repeated sampling of stroke lesion volume in this study, the late reduction in lesion size seems most likely due to reabsorption of necrotic tissue in the interval before the final follow-up scan is performed. The effect of tissue reabsorption in reducing the final stroke size to less than the initial stroke size may be more apparent in this study for 2 reasons. First, a significant proportion of patients in this cohort had small-vessel strokes with small absolute lesion volumes (Figure 5). Second, in 2 patients with large-vessel MCA strokes, early reperfusion prevented significant growth of the lesion volume (Figure 5). Since the largest increases in lesion size between the initial and follow-up MR scans occur more commonly in proximal large-artery occlusions than in branch artery occlusions, the effects of tissue reabsorption on percent change in stroke size may be more prominent in smaller strokes.
In 3 patients, a rise and fall in lesion volume over the first 2 weeks was documented, suggesting that edema contributed to lesion volume growth. Edema following ischemic stroke develops as early as 4 to 15 hours, peaks at 48 to 96 hours, and generally resolves by 6 days.22,23 In contrast, in 6 patients (patients 2, 5, 6, 11, 13, and 14) lesion volumes increased acutely but then plateaued over the ensuing days or weeks, suggesting that edema was not a major contributing factor to the increase in lesion size. Previous DWI studies have analyzed the change in lesion volume as defined by 2 time points. The biphasic nature of the curves of lesion volume over time in our study (Figure 6) shows that this difference will depend on the timing of both the final and initial scans. Because a primary expansion of ischemic injury, as well as secondary processes such as ischemic swelling and reabsorption of necrotic tissue, can affect lesion size, establishing the “gold standard” stroke size in a group of patients is a challenging task. Blocking the growth of DWI lesion volume in the first 24 hours after stroke onset remains a very appealing target for therapeutic strategies. However, because of the confounding factors of edema and tissue loss, future efforts may require the development of more sophisticated measures of remaining normal brain volumes.

A fall in the ADC of water has been shown to occur shortly after onset of ischemia in animal stroke models. This decrease contributes to the increased hyperintensity on DWI and is regarded as a marker of cytotoxic edema. Vasogenic edema, as may surround tumors, causes an opposite effect, ie, an increase in ADC values. A pattern of rapid evolution of ADC has been described in animal stroke models, in which values fall to a nadir, then increase to pseudo-normal and then above normal levels over 24 to 48 hours.24,25 Studies using data from many stroke patients scanned at varying intervals after symptom onset have suggested in humans a more persistent reduction in ADC lasting days, with pseudo-normalization and elevated ADC further delayed by a week or more.14,17

In this study we identify the time course of ADCr changes in individual human cases scanned repeatedly over time. It is important to note that our analysis of ADCr uses a mean value of all pixels that are contained within the volume of DWI signal abnormality. Regional heterogeneity of ADC values can occur within the lesion volume, and this is not specifically addressed in our analysis beyond the impact such heterogeneity would have on mean ADCr values. The results from our serial studies demonstrate that mean relative ADC (ADCr) is often close to its lowest value at the earliest time point (mean, 7.6 hours) (Figure 2). However, a further fall in ADCr on subsequent scans in the next 24 hours occurred in most patients, and the measured mean ADCr nadir in our series was not seen until 32 hours from symptom onset. ADCr values were frequently above their nadir on scans performed at 1 to 2 weeks after stroke onset but were still below normal. Among 73 observations, ADCr >1 never occurred before 17 days. Even in cases with suspected early ischemic edema (patients 1, 4, 9, and 10), the ADCr remained below normal. Moreover, in 13 of 14 patients T2 lesion volume increased while ADCr decreased.

Preventing progressive fall of ADCr in human stroke may represent 1 surrogate imaging end point for evaluating the efficacy of neuroprotective therapies. This would be a more attractive target for therapy if the fall were more robust in those patients who are scanned earlier after symptom onset or in those with larger infarcts. An initial low ADCr correlated with a higher (ie, poorer) NIHSS and might reflect more complete initial ischemia with a worse long-term outcome. Future studies could examine whether regions of low ADCr reflect more severe ischemic injury and carry an increased risk for hemorrhage after thrombolysis.

HWI delineates regions of abnormal cerebral perfusion. We and others6–8 have shown in human large-vessel stroke
that the region of brain ischemia by HWI is often larger than the region of ischemic injury as defined by increased DWI signal intensity. This mismatch between the volume of ischemic injury and the larger volume of ischemic brain may represent tissue at risk but inherently salvageable by reperfusion. In this report abnormal regions of CBV are reported. While other measures of hemodynamic imaging were calculated, including relative cerebral blood flow and relative mean transit time maps, they are the subject of an ongoing analysis.

The small number of patients in this study who had large strokes without early spontaneous reperfusion precludes a detailed analysis of CBV change over time. The initial CBV only slightly overestimated the largest T2 infarct volume. Dramatic reduction in the volume of tissue with relative CBV hypointensity over serial scans documents reperfusion, which was corroborated by 2-dimensional phase-contrast MR angiography. In the 5 patients with MCA stroke, the 2 patients who showed early reperfusion (patients 7 and 13) had significantly smaller final infarct volumes and better clinical outcomes than the 3 patients with late or no reperfusion. The patient with maximum lesion volume on initial scan (patient 7, Figure 7) also had early spontaneous reperfusion. The ability to document by MRI this “reperfusion rescue” might provide a mechanism for evaluating therapies designed to optimize reperfusion and minimize reperfusion injury.

This study confirms that hyperacute MR scanning with repeated imaging is feasible (total imaging time, 35 minutes) and provides valuable information that may help guide therapy. Although the numbers of patients are small and factors such as age and stroke location are important, initial DWI lesion volume correlated well with maximum T2 volume (r=0.97; P<.001) and, more importantly, with clinical outcome as assessed by the final NIHSSS at follow-up (r=0.77; P<0.01). This effect has also been seen in 2 recent series, reported by Lovblad et al.26 and Tong et al.27 The effect on outcome is not surprising, since larger MCA strokes are expected to result in a worse outcome than smaller MCA strokes or small-vessel occlusive strokes. Within the group B patients with deep penetrator stroke, location may be a better predictor of deficit, and we found no significant correlation between lesion size and NIHSSS.

Given the vast array of neuroprotective agents in preclinical trials, there is a great demand for techniques that permit rapid diagnostic assessment and identify markers of biological effect. In the early hours after symptom onset, it is extremely desirable to be able to distinguish large-vessel from small-vessel ischemia, to identify penumbral territory at risk, and to better predict clinical outcome in a conventionally treated population. Here we have shown that DWI and HWI offer means to measure biological markers of infarct development including (1) rate and progression of lesion growth, (2) rate and depth of ADC reduction in the lesion, and (3) tissue reperfusion. DWI and HWI provide this information within minutes and may permit more effective patient selection for particular therapies and improve evaluation of experimental therapeutic strategies. Our data indicate that it is common to see continued worsening of both the ischemic lesion volume on DWI and the ischemic tissue characteristics (as measured by the ADCr, T2) hours to days after onset of symptoms. In addition to expansion of the primary ischemic injury, secondary processes contribute to changes in lesion size. In some patients an early decrease in lesion volume may occur as edema resolves, and in most patients a late decrease in lesion size occurs, likely due to reabsorption of necrotic tissue. Combined with data showing the evolution of ischemic infarction in patients with the use of PET3 and MR studies showing expansion of lesion size by DWI,6,7 these data suggest that MR can be used to follow the progression of stroke in the acute phase, characterize different patient populations, and provide targets for neuroprotective therapies.

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References


Time Course of Lesion Development in Patients With Acute Stroke: Serial Diffusion- and Hemodynamic-Weighted Magnetic Resonance Imaging

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