Persistent Infarct Hyperintensity on Diffusion-Weighted Imaging
Late After Stroke Indicates Heterogeneous, Delayed, Infarct Evolution

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Background and Purpose—Some infarcts have persistently hyperintense areas on diffusion-weighted MRI (DWI) even at 1 month after stroke, whereas others have become isointense to normal brain. We hypothesized that late DWI hyperintensity reflected different infarct evolution compared with areas that were isointense by 1 month.

Methods—We recruited patients prospectively with ischemic stroke, performed DWI and perfusion-weighted MRI (PWI) on admission, at 5 days, 14 days, and 1 month after stroke, and assessed functional outcome at 3 months (Rankin Scale). Patient characteristics and DWI/PWI values were compared for patients with or without “still hyperintense” infarct areas on 1-month DWI.

Results—Among 42 patients, 27 (64%) had “still hyperintense” infarct regions at 1 month, mostly in white matter. Patients with “still hyperintense” regions at 1 month had lower baseline apparent diffusion coefficient ratio (ADCr; mean ± SD 0.76 ± 0.12 versus 0.85 ± 0.12; hyperintense versus isointense; P < 0.05), prolonged reduction of ADCr (repeated-measures ANOVA; P < 0.01), no difference in baseline perfusion but delayed normalization of mean transit time (P < 0.05) and cerebral blood flow ratios (repeated measures ANOVA; P < 0.05), initially more severe stroke, and worse 3-month outcome than patients whose lesions were isointense by 1 month.

Conclusion—The late DWI lesion hyperintensity emphasizes the heterogeneity in temporal evolution of stroke injury and suggests ongoing “ischemia.” Lower baseline ADCr precedes delayed perfusion normalization, suggesting that worse cell swelling impedes reperfusion. Further study is required to determine underlying mechanisms and any potential for subacute intervention to improve recovery. (Stroke. 2006;37:1418-1423.)

Key Words: cerebrovascular disorders ■ magnetic resonance imaging ■ magnetic resonance imaging, diffusion-weighted ■ magnetic resonance imaging, perfusion-weighted ■ stroke

Most interest to date in magnetic resonance diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) has been on their use as a diagnostic tool in hyperacute stroke (eg, to distinguish transiently from permanently damaged tissue or as a surrogate marker for effectiveness of new treatments). The evolution of DWI/PWI lesion appearances during subacute and later stages after stroke, and the relationship to underlying tissue perfusion, has received less attention.

The infarct appearance on DWI is influenced mainly by the apparent diffusion coefficient (ADC) and T2 relaxation time of the tissue. The ischemic lesion becomes hyperintense on DWI relative to normal tissue within minutes of injury in experimental models and within hours of stroke onset in patients (Figures 1 and 2). In this acute stage, hyperintensity on DWI is mainly caused by a decrease in ADC, whereas T2 relaxation remains relatively normal. Subacutely, the ADC gradually increases to or above normal, usually by 2 weeks. Hypointensity seen thereafter on DWI has been attributed to increased T2 relaxation of the tissue (T2 “shine through”); Figure 2), thought to reflect increased extracellular water content from vasogenic edema. DWI hyperintensity can become isointense or hypointense to normal tissue within 15 days but sometimes takes as long as 57 to 72 days, depending on the population, with persistent DWI hyperintensity at these late times being attributed to T2 “shine through.”

We observed that in some patients, all DWI hyperintensity had resolved by 1 month (Figure 1), whereas in other patients, parts of some infarcts remained hyperintense on DWI at 1 month or later after stroke (Figure 2), and other parts of the infarcts did not. We also noted (as in Figure 2) that there was persistent hypointensity on the ADC map at 1 month in the infarct in some patients but not others (Figure 1). This suggested that some...
infarcts underwent different patterns of evolution to others. If persistent hyperintensity at later times were solely a $T_2$ “shine through” effect, yet most old infarcts are hyperintense on $T_2$-weighted ($T_2\text{W}$) imaging, why were only some parts of some infarcts hyperintense on DWI in only some patients?

We hypothesized that regions of infarcts remaining hyperintense late after stroke might have distinct pathophysiology, such as delayed onset of ischemia, prolonged ischemia, or altered repair processes compared with infarcts (or parts of infarcts) not remaining hyperintense. Evidence of prolonged tissue ischemia or repair might offer the possibility of developing strategies for enhancing repair or preventing further damage in the subacute stage after stroke. Treatment strategies for acute ischemic stroke to date focus on starting treatment as fast as possible, presupposing that all, or virtually all, of the damage from the stroke occurs within the first

Figure 1. DWI, ADC, and $T_2\text{W}$ images at 6 hours (h), 6 days (d), 13 days, and 1 month (mo). DWI is hyperintense to normal tissue at 6 hours and decreases to become isointense or hypointense to normal tissue by 2 weeks.

Figure 2. DWI, ADC, and $T_2\text{W}$ images at 3 hours (h), 7 days (d), 14 days, and 1 month (mo). DWI at 1 month shows a “still hyperintense” region of infarct, corresponding to a region of hypointensity on the ADC image.
few hours, yet ischemic but viable tissue exists at later time points, and other processes might occur subacutely that could further add to the burden of damage.

We therefore examined the DWI and dynamic susceptibility contrast PWI of patients all imaged from acute (<24 hours maximum) to late (1 month) stages to determine whether DWI and PWI values were different in the infarct regions remaining hyperintense on DWI compared with those that became isointense by 1 month after stroke.

Materials and Methods

Patients

Patients, prospectively recruited from the hospital inpatient stroke service with all severities of ischemic stroke, were imaged as soon as possible but within a maximum of 24 hours from stroke onset. Baseline clinical assessment and stroke scoring, including the National Institutes of Health Stroke Score (NIHSS) and Oxfordshire Community Stroke Project (OCSP) classification, were performed by a trained stroke physician. Functional outcome (modified Rankin Scale [mRS]) was assessed at 3 months. All clinical and imaging assessments and analyses were performed blinded to each other.

DWI and PWI

Imaging was performed within 24 hours (baseline) and repeated at 5 days, 14 days, and 1 month after stroke onset on a GE Sigma LX 1.5T (General Electric) clinical magnetic resonance scanner, equipped with a self-shielding gradient set (22 mT/m maximum gradient strength and 120 T/m/s slew rate) and manufacturer-supplied “birdcage” quadrature head coil. The MRI examination included a standard fast spin-echo T2W sequence, a gradient-echo T1-weighted sequence, a diffusion tensor (DT-MRI) spin-echo echo-planar (EP) imaging, and dynamic susceptibility contrast PWI. In the DT-MRI protocol, sets of axial diffusion-weighted EP images (b=0 and 1000 s/mm²) were collected with diffusion gradients applied sequentially along 6 noncollinear directions. Five acquisitions consisting of a baseline T2W EP image and 6 diffusion-weighted EP images (total 35 images) were collected per slice position. Cerebral perfusion was measured by tracking a bolus of gadolinium diethylenetriamine pentaacetic acid for 85 s using a single-shot gradient-echo EP sequence. The diffusion and perfusion EP sequences shared these acquisition parameters: 15 axial slices, 5-mm slice thickness, 1-mm slice gap, 128×128 image matrix, and 24×24 cm field of view.

We ensured that slice locations used in the follow-up scans corresponded as closely as possible to those in the first by recording the subject’s head position and tilt in the first scan and repositioning the patient identically in the follow-up scans. We also used computational techniques to realign the diffusion- and perfusion-weighted EP images in the follow-up scans to the first, thereby removing many small remaining positioning errors, bulk patient motion, and eddy current–induced artifacts.

Quantitative cerebral perfusion parameters were calculated in each voxel from the signal intensities in the component EP images. Maps of T2W signal intensity, mean transit time (MTT [from the first moment of the concentration time curve]), and cerebral blood flow (CBF [calculated from area under the curve/MTT]) for every patient at each time point were generated on a voxel-by-voxel basis and converted into Analyze (Mayo Foundation) format.

DWI and PWI Lesion Analysis

We manually outlined the visibly abnormal acute lesion on the baseline DWI on a Sun Ultra Sparc Station 10 (Sun Microsystems) in Analyzeformat. Image brightness and contrast were adjusted for optimal contrast between hyperintense tissue and normal-appearing brain. A contralateral region of interest, equal in size and position to the lesion, was drawn to act as a normal control area.

The 1-month DWI scans were assessed for “still hyperintense” regions, defined as areas of persistent hyperintensity compared with the rest of the visible lesion (Figure 2), by a neuroradiologist blind to all other information. Patients with persistent hyperintensity on 1-month DWI were called “still hyperintense,” and patients with isointense or hypointense lesions on 1-month DWI were called “isointense” (Figure 1). In patients with “still hyperintense” infarct regions at 1 month, other areas of the original infarct that were not still hyperintense (ie, were isointense) were referred to as “not still hyperintense.”

Areas of persistent hyperintensity on 1-month DWI were separately outlined (with homologous contralateral regions for comparison). Baseline DWI infarct regions and regions appearing “still hyperintense” at 1 month were applied to the scans from 5 days, 14 days, and 1 month. All lesions on subsequent scans were checked to ensure they were original lesions and not the result of new ischemic events. Patients with no persistent hyperintensity on 1-month DWI had only baseline scan infarct regions applied to the scans from 5 days, 14 days, and 1 month.

ADC, CBF, and MTT values were extracted for all areas traced at all time points, and relative values (ADC ratio [ADCr], CBF ratio [CBFr], and MTT ratio [MTTr]) to adjust for any between-scan machine differences were calculated by dividing the ipsilateral values by the corresponding contralateral values. We did not extract T1 data because more complex imaging would have been required for reliable results that would have significantly prolonged the scan time.

Lesion Composition Analysis

A neuroradiologist blind to all other details scored the baseline lesion as comprising of gray matter, white matter, or both. If present, the “still hyperintense” region on the 1-month DWI was also scored as comprising gray matter, white matter, or both. Finally, the 1-month scan was compared with the baseline scan to determine whether the hyperintensity at 1 month had been within the original boundary of the ischemic lesion at baseline or was a subsequently developing new area of infarction.

Statistical Analyses

Clinical details were compared using standard t tests for normally distributed data (age, time of baseline scan), Mann–Whitney U tests for nonparametric data (baseline NIHSS, outcome mRS), and χ² tests for categorical data (sex, mRS of 0 to 2 or 3 to 6, OCSP classification). To test whether persistent hyperintensity reflected an initial difference or prolonged ADC abnormality, standard t tests (paired for comparing regions within “still hyperintense” patients; unpaired for the 2 region types in “still hyperintense” patients versus “isointense” patients) were performed for ADCr values at baseline and 1 month, CBFr and MTT values at baseline and 5 days, the peak CBFr and nadir MTT values and its timing were also compared with identify perfusion differences in tissue destined to be “still hyperintense” versus “isointense” early after the stroke. General linear model (GLM) repeated-measures regression analysis (ANOVA) was performed to compare ADCr, CBFr, and MTT over time from baseline to 1 month (dependent variables ADCr, CBFr, and MTT values; ADCr and MTT fit to a linear model; CBFr fit to a quadratic model) between patients with “isointense” infarcts at 1 month and patients with “still hyperintense” infarcts, in the latter, both in areas that remained hyperintense and those that became isointense. ADCr, CBFr, and MTT values are reported as mean±SD. All analyses were performed in SPSS for Windows (version 11.0.0; SPSS Inc).

Results

Patients

Forty-two patients with MRI data at all 4 time points up to 1 month were included: 23 of 42 (55%) were male with an average age of 71 years (range 36 to 93 years). Mean NIHSS score on admission was 9 (median 7; range 1 to 25). OCSP classifications: 13 of 42 (31%) patients had a total anterior circulation infarct, 25 of 42 (60%) had a partial anterior circulation infarct, 3 of 42 (7%) had a lacunar infarct, and 1 of 46 (2%) had a posterior circulation infarct. Sixteen patients...
(38%) were imaged within 6 hours, 11 of 42 (26%) patients between 6 and 12 hours, and 15 of 42 (37%) patients between 12 and 24 hours after stroke onset, and mean±SD time from stroke onset to baseline MRI 10±7 hours. At 3 months, 14 of 42 (33%) patients were dead or dependent (mRS 3 to 6).

On 1-month DWI, 27 of 42 (64%) patients had “still hyperintense” infarct regions. Sex and age did not significantly differ between “still hyperintense” and “isoointense” patients. Clinically, “still hyperintense” patients had a higher NIHSS score on admission (median 9 versus 4; P<0.01) and were more likely to be dead or dependent (mRS 3 to 6; P<0.05) than “isoointense” patients. “Still hyperintense” patients had their initial MRI scan later than “isoointense” patients (mean 12 hours versus 7 hours; P<0.03), with no differences in timing of subsequent scans. All regions remaining hyperintense on 1-month DWI were within the baseline lesion. Baseline DWI lesion volumes in “still hyperintense” patients were larger (median 17.8; range 3.2 to 154.5 cm³) than in “isoointense” patients (median 8.4; range 0.6 to 87.0 cm³; P<0.01; Table).

### ADCr From Baseline to 1 Month

In “still hyperintense” patients, ADCr at baseline was significantly lower both in “still hyperintense” (ADCr 0.760±0.122) and “not still hyperintense” regions (ADCr 0.734±0.110) than in the infarct region in “isoointense” patients (ADCr 0.850±0.123; P<0.05 and P<0.01, respectively; Figure 3). The lower baseline ADCr in “still hyperintense” lesion areas remained lower over time compared with lesion areas in “isoointense” patients (ADCr 0.850±0.123; P<0.05 and P<0.01, respectively; Figure 3). At 1 month, ADCr values were significantly lower in “still hyperintense” regions (ADCr 1.012±0.206) compared with “not still hyperintense” regions in “still hyperintense” patients (ADCr 1.289±0.229; P<0.01) and the infarct in “isoointense” patients (ADCr 1.209±0.157; P<0.01). Within patients with “still hyperintense” lesion areas, ADCr in areas “not still hyperintense” increased more rapidly than in “still hyperintense” tissue from 2 weeks onward (P<0.01; Figure 3).

### CBFr and MTTr From Baseline to 1 Month

There was no difference in CBFr or MTTr at baseline between the 3 groups (t tests all P=NS). However, MTTr at 5 days was significantly prolonged in the “still hyperintense” regions (MTTr 1.251±0.470) compared with “isoointense” patients (MTTr 1.035±0.074; P<0.05; Figure 3) and CBFr in “still hyperintense” tissue took longer to reach a peak and return to normal than in “not still hyperintense” areas (GLM regression P<0.05; Figure 3).

### Lesion Composition Analysis

At baseline, 4 infarcts involved only gray matter, 5 involved only white matter, and 33 were in gray and white matter. “Still hyperintense” regions on 1-month DWI were almost exclusively in white matter (25 of 27; 92%), only 1 of 27 (4%) were in gray matter, and 1 of 27 (4%) were in both gray and white matter. Gray matter–only lesions were in all “isoointense” patients (4 of 4), whereas most white matter only lesions were in “still hyperintense” patients (4 of 5; 80%).

### Discussion

These data indicate that tissue that is persistently hyperintense on DWI at 1 month is biologically different to isoointense areas, this difference occurred for ADCr from baseline and for perfusion values from 5 days onward, and the evolution of cellular changes within the infarct was heterogeneous.

What underlying pathophysiological process might account for these observations? The perfusion values were the same at baseline in all ischemic tissues but showed delayed recovery in “still hyperintense” tissue. This could be a consequence of the more abnormal ADCr values (if, for example, persistent cell swelling impeded blood flow in microvessels) or a cause (if persistently abnormal perfusion delayed tissue repair). “Still hyperintense” lesions were larger than “isoointense” at baseline, possibly increasing the chance of reperfusion failing to reach some parts of the infarct. Perhaps this is the magnetic resonance equivalent of the “poor reflow phenomenon” or some other factor that contributes to slower recovery of blood flow, hence possibly prolonging ischemia or delaying lesion repair. Reasons for the “poor reflow phenomenon” are not well understood; perhaps the areas have different inflammatory responses or blood–brain barrier damage that contribute to persistent cell swelling. Also, although early reperfusion is associated with rapid return of ADC values to normal, little is known about the influence of perfusion changes occurring at later times. Perhaps greater initial cell swelling (consistent with the marginally lower baseline ADCr in tissue destined to be still hyperintense) delays reperfusion at the tissue level (possibly separate from changes in the main arteries) so it may slow recovery and could also partially explain our observed association with worse functional outcome. This interpretation of the order of events implies that poor reperfusion may in turn perpetuate persistent cellular abnormalities in the brain, so delaying recovery: a vicious cycle.

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### Baseline Features of Patients With Tissue That Was “Still Hyperintense” or “Isoointense” on DWI at 1 Month After Stroke

<table>
<thead>
<tr>
<th>Feature</th>
<th>Still Hyperintense</th>
<th>Isoointense</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>27</td>
<td>15</td>
</tr>
<tr>
<td>DWI lesion volume (cm³)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>32.26</td>
<td>19.90</td>
</tr>
<tr>
<td>Median</td>
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<td>8.43</td>
</tr>
<tr>
<td>Minimum</td>
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<td>0.60</td>
</tr>
<tr>
<td>Maximum</td>
<td>154.50</td>
<td>87.10</td>
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<tr>
<td>OCSP classification</td>
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<td></td>
</tr>
<tr>
<td>TACS</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>PACS</td>
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<td>10</td>
</tr>
<tr>
<td>LACS</td>
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<td>2</td>
</tr>
<tr>
<td>POCS</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Age (range) years</td>
<td>73 (36–93)</td>
<td>69 (39–87)</td>
</tr>
<tr>
<td>NIHSS (mean)</td>
<td>9 (3–25)</td>
<td>4 (1–14)</td>
</tr>
</tbody>
</table>

OCSP classification, TACS indicates total anterior circulation syndrome; PACS, partial anterior circulation syndrome; LACS, lacunar syndrome; POCS, posterior circulation syndrome.
Figure 3. ADCr (A), CBFr (B), and MTTr (C) for all time points. SH indicates tissue remaining “still hyperintense”; NSH, rest of the baseline DWI lesion in “still hyperintense” patients (n=27) followed through subsequent scans; ISO, tissue from the baseline DWI lesion in “isointense” patients (n=15) followed through subsequent scans. Error bars represent ±1 SD.
These data also provide further evidence for differences in the ADC response to ischemia between gray and white matter. In the current study, the late hyperintense regions were almost exclusively in white matter, suggesting that differential evolution of ischemia between gray and white matter observed within the first 24 hours\(^2\) and 14 days\(^2\) persists to later times. Several other studies suggest (indirectly) that persistent DWI hyperintensity may occur in specific infarct locations, mostly small subcortical white matter lesions. Small lacunar infarcts may remain hyperintense on DWI for longer periods (54 to 144 days) than larger infarcts.\(^23\) Late DWI hyperintensity (at a mean of 21 days) was correlated with higher age and NIHSS in patients with mild strokes.\(^24\) These studies drew attention to the existence of late DWI hyperintensity but did not determine the pattern of early infarct evolution or perfusion.

Possible limitations of the present study include the subjective method of deciding which tissue was “still hyperintense” on 1-month DWI, a judgment made by visually examining the relative signal hyperintensities of the DWI lesion. If areas clearly stood out from the background by being hyperintense relative to the rest of the infarct or to normal brain, then they were classed as “still hyperintense” (Figures 1 and 2). We did not use a threshold of DWI signal intensity or ADC value specifically to avoid the problem of masking any important tissue differences that might have occurred by imposing fixed arbitrary values. We used relative perfusion values that may have masked some subtle between-patient differences. However, we used ratios to limit the impact of any between-patient and between-scan differences. The “still hyperintense” group had baseline imaging a little later than the “isointense” group (they had more severe strokes and took longer to prepare for scanning), but all subsequent imaging times were the same for the 2 groups, so we do not think that this will have affected the analyses.

If persistent DWI hyperintensity does mean slower “evolution” of ischemic tissue repair, then the opportunity might exist to intervene in some way to prevent further insults, even late after stroke. Efforts to improve flow in the microvessels, even subacutely, possibly by reducing cell swelling and ongoing microvascular thrombosis, could help improve reperfusion, perhaps speed up tissue repair, prevent further recruitment of viable tissue into the infarct, reduce inflammation, and possibly lead to better functional outcomes. Therefore, tissue remaining hyperintense on late DWI should not just be dismissed as areas of T₂⁺-shine through.” Further study is required to determine what these “still hyperintense” lesion areas mean in terms of pathophysiological changes at the tissue level and clinical recovery and whether any later intervention could improve outcome.

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References

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