Dynamic Evolution of Diffusion-Weighted Imaging Lesions in Patients With Minor Ischemic Stroke

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Background and Purpose—Diffusion-weighted imaging (DWI) lesion volume on magnetic resonance imaging is increasingly being used as a surrogate outcome measure in clinical trials. We aimed to characterize the evolution of DWI lesion volumes within 30 days of symptom onset after minor stroke.

Methods—Minor stroke patients with DWI lesions on magnetic resonance imaging within 48 hours of symptom onset were prospectively followed with magnetic resonance imaging brain scan at 7 and 30 days. Change in the lesion volume was defined as the difference between day 30 Fluid-Attenuated Inversion Recovery and baseline DWI lesion volumes.

Results—Three patterns of infarct evolution were observed: reduction (72 [63%]), no change (26 [23%]), and growth (16 [14%]). Patients with infarct reduction at 30 days had larger baseline DWI lesion volumes (2.5 [0.9–8.5] mL) than those with stable infarcts (0.5 [0.3–0.9] mL; P=0.01). Complete DWI reversal at day 30, was seen in only 6 (5.3%) patients.

Conclusions—The most common pattern of infarct evolution in patients with minor stroke is a reduction in volume, but complete resolution is uncommon. (Stroke. 2015;46:000-000. DOI: 10.1161/STROKEAHA.115.009775.)

Key Words: brain infarction • diffusion-weighted magnetic resonance imaging • stroke

Infarct volume is an important predictor of poststroke functional disability. Final infarct volume may be assessed early (<1 week) or late (90 days). One third of patients with visible infarcts on acute diffusion-weighted imaging (DWI) no longer have identifiable ischemic lesions at day 90. The temporal profile of this apparent reversal within the 90 days is unknown.

Infarct volumes on magnetic resonance imaging (MRI) are increasingly used as surrogate outcome measures, in particular trials involving patients with minor ischemic events. These end points may be affected by the timing of the acquisition of the MRI scan. Using a serial imaging approach, we aimed to characterize the evolution of DWI lesion volumes within 30 days of minor stroke.

Methods

Patients
Adult minor ischemic stroke (defined as National Institute of Health Stroke Scale [NIHSS] ≤3) patients were prospectively enrolled within 48 hours of symptom onset.

Imaging Protocol
All patients underwent serial MRI (1.5T) brain scans within 48 hours of symptom onset, at 7 and 30 days. The MRI protocol consisted of DWI, Fluid-Attenuated Inversion Recovery (FLAIR), time-of-flight MR angiography and gradient recalled echo sequences.

Image Analysis
Diffusion-restricted lesion volumes were measured using ANALYZE (12.0) on DWI and FLAIR images by 2 blinded raters (M.K. and P.R.; interclass correlation coefficient, 0.95; mean difference, 0.2±0.5 mL) using a semiautomated threshold technique. Lesion locations were categorized as isolated cortical, isolated subcortical, or combined. Previous infarcts, hemorrhagic transformation, microbleeds and new radiographic lesions on follow-up imaging were also recorded.

Change in infarct volume was defined as the difference between the 30-day FLAIR lesion volume and baseline DWI lesion volume. On the basis of the results of a previous inter-rater DWI lesion measurement study, infarct growth was defined as an absolute increase in infarct volume of >0.3 mL. A decrease in infarct volume >0.3 mL was defined as infarct reduction. Any volume change <0.3 mL was defined as a stable infarct. In cases with complete lesion resolution on T2 and FLAIR at day 30, a 3-dimensional–voxel coregistration between the baseline DWI and follow-up images was performed; these patients were considered complete reversal.

Statistical Analysis
Differences in age, relative apparent diffusion coefficient, and duration between onset-baseline MRI was tested with 1-way ANOVA. Non-normally distributed DWI and FLAIR lesion volume differences between groups were assessed with an ANOVA on ranks, followed by post hoc Kruskal–Wallis tests. Predictors of excellent functional
outcome (modified Rankin Score ≤ 1) were assessed using logistic regression adjusting for age and baseline lesion volume.

**Results**
A total of 196 patients were screened with MRI, 114 (58.2%) had baseline DWI lesions and were included for further analysis (Table 1).

### Temporal Evolution
Infarct reduction was seen in 43% (n=49) of patients at day 7 (Figure I in the online-only Data Supplement) and 63% (n=72) of patients at day 30 (Table 2). Infarct growth occurred in 25% (n=29) of patients at day 7 and 14% (n=16) of patients at day 30. Stable infarct volumes were seen in 31% (n=36) of patients at day 7 and 23% (n=26) of patients at day 30 (Figure). Patients with infarct reduction at 30 days had larger baseline DWI lesion volumes (2.5 [0.9–8.5] mL; P=0.01) than those with stable infarcts (0.5 [0.3–0.9] mL; P=0.01). Patients with infarct growth also had larger baseline DWI lesion volumes (2.4 [0.9–9] mL; P<0.0001). In the 6 (5.3%) patients with complete lesion reversal at 30 days, this was already evident in 5 of them at 1 week. The mean baseline relative apparent diffusion coefficient in DWI lesions with complete reversal was higher (0.96±0.1 mL) than all other patients (0.86±0.1; P=0.04). Isolated cortical location of DWI lesion was more frequent in patients with complete reversal (n=4/6) than all other patients (n=19/108; odds ratio, 9.3, [1.5, 55]).

### Clinical Outcome
There was no difference in the median 90-day modified Rankin Score in the different evolution categories (infarct reduction: 0.5 [0–2], infarct growth: 1 [0–2], and stable infarct: 1 [0–2]; P=0.9). Infarct evolution category was not associated with excellent functional outcome at 90 days (odds ratio, 0.8, [0.2, 2.6]). Baseline median NIHSS, however, was independently associated with (odds ratio, 1.6, [1.1, 2.3]) excellent functional outcome at 90 days.

### Discussion
In minor stroke patients with DWI lesions at baseline more than half undergo infarct volume reduction within the first month, however, complete reversal is rare. A qualitative minor stroke imaging study reported that when MRI scans were assessed at 90 days, one third of infarcts identified acutely using DWI, were no longer visible. Although we found that apparent complete reversal was less common at 30 days (5%), an infarct volume decrease was actually more frequent (63%). This is consistent with another study assessing evolution of lacunar infarcts, indicating that acute DWI lesions overestimate the final infarct volume by 40%.

In the patients with complete DWI reversal, we cannot exclude the possibility that no tissue was actually infarcted at the time of baseline MRI scans. Alternatively, it may be that the true final infarct volume is actually not zero in most of these patients. Instead, reduction in infarct volume probably reflects differences in the sensitivity of the different MRI sequences to acute, subacute, and chronic infarction.

### Limitations
This study is limited by small sample size. In addition, the slice thickness of all sequences was 5 mm, which is relatively low resolution. Although DWI is sensitive to acute infarction even at this resolution, tissue volume loss and partial volume

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**Table 1. Clinical Characteristics in Different Infarct Evolution Categories**

<table>
<thead>
<tr>
<th>Infarct Evolution</th>
<th>Infarct Reduction (n=72)</th>
<th>Infarct Growth (n=16)</th>
<th>Stable Infarct (n=26)</th>
<th>Total (n=114)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>65 (56–77)</td>
<td>70 (61–78)</td>
<td>65 (59–78)</td>
<td>66.1 (58–77)</td>
<td>0.9</td>
</tr>
<tr>
<td>Male†</td>
<td>48 (66.7)</td>
<td>11 (68.8)</td>
<td>18 (69.2)</td>
<td>77 (67.5)</td>
<td>0.9</td>
</tr>
<tr>
<td>Baseline NIHSS*</td>
<td>1 (0–2)</td>
<td>1 (0–3)</td>
<td>2 (0–3)</td>
<td>1 (0–3)</td>
<td>0.2</td>
</tr>
<tr>
<td>ABCD2 Score*</td>
<td>5 (4–6)</td>
<td>5 (4–6)</td>
<td>5 (5–6)</td>
<td>5 (4–6)</td>
<td>0.5</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension†</td>
<td>41 (56.9)</td>
<td>8 (50)</td>
<td>14 (53.8)</td>
<td>63 (55.3)</td>
<td>0.6</td>
</tr>
<tr>
<td>Diabetes mellitus†</td>
<td>9 (12.5)</td>
<td>2 (12.5)</td>
<td>5 (19.2)</td>
<td>16 (14)</td>
<td>0.7</td>
</tr>
<tr>
<td>Dyslipidemia†</td>
<td>34 (47.2)</td>
<td>8 (50)</td>
<td>13 (50)</td>
<td>55 (48.2)</td>
<td>0.9</td>
</tr>
<tr>
<td>Stroke cause</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large-artery-atherosclerosis†</td>
<td>14 (19.4)</td>
<td>4 (25)</td>
<td>9 (34.6)</td>
<td>27 (23.7)</td>
<td>0.3</td>
</tr>
<tr>
<td>Cardioembolic†</td>
<td>24 (33.3)</td>
<td>5 (31.3)</td>
<td>4 (15.4)</td>
<td>33 (28.9)</td>
<td>0.2</td>
</tr>
<tr>
<td>Small vessel disease†</td>
<td>7 (9.7)</td>
<td>2 (12.5)</td>
<td>5 (19.2)</td>
<td>14 (12.3)</td>
<td>0.4</td>
</tr>
<tr>
<td>Symptoms duration &lt;24 h†</td>
<td>14 (19.4)</td>
<td>2 (12.5)</td>
<td>11 (42.3)</td>
<td>27 (23.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Dual antiplatelet therapy†</td>
<td>8 (11.1)</td>
<td>0 (0)</td>
<td>2 (9.2)</td>
<td>10 (7.6)</td>
<td>0.2</td>
</tr>
<tr>
<td>Anticoagulant therapy†</td>
<td>19 (26.4)</td>
<td>1 (6.3)</td>
<td>5 (19.2)</td>
<td>25 (21.9)</td>
<td>0.2</td>
</tr>
<tr>
<td>Hospital stay in d*</td>
<td>3.9 (1.5–4.9)</td>
<td>2.8 (1.5–4.9)</td>
<td>0.6 (0.4–4.5)</td>
<td>3.2 (0.7–5.7)</td>
<td>0.053</td>
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<tr>
<td>mRS at 90 days*</td>
<td>0.5 (0–2)</td>
<td>1 (0–2)</td>
<td>1 (0–2)</td>
<td>1 (0–2)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

*ABCD2 indicates Age, Blood pressure, Clinical symptoms, Duration of symptoms and Diabetes; mRS, modified Rankin Score; and NIHSS, National Institute of Health Stroke Scale.  
*Median (interquartile range).  
†n (%).
Conclusions

The most common pattern of infarct evolution in patients with minor stroke is a reduction in volume. The majority of infarct volume reduction occurs by 7 days after symptom onset, but complete resolution is uncommon.

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Dr. Butcher holds a Canada Research Chair in Cerebrovascular Disease and the Heart and Stroke Foundation of Alberta Professorship.

Figure

Four evolution patterns of DWI (diffusion-weighted imaging) lesions after minor ischemic stroke. ADC indicates apparent diffusion coefficient; and FLAIR, Fluid-Attenuated Inversion Recovery.
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Disclosures

None.

References


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Supplemental Figure I: Infarct evolution pattern at 7 days and 30 days.