Predictors of Apparent Diffusion Coefficient Normalization in Stroke Patients

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Background and Purpose—We sought to describe the frequency of normalization of apparent diffusion coefficient (ADC) values that are decreased in hyperacute stroke and to identify characteristics of tissue demonstrating normalization.

Methods—Sixty-eight acute ischemic stroke patients underwent MRI examination (including diffusion/perfusion imaging and MR angiography) within 6 hours (mean, 2.8 hours) after symptom onset, after 24 hours, and again 4 to 7 days later. Lesion volumes with decreased ADC and delayed time to peak in perfusion imaging were determined. In patients showing ADC normalization, volumes with ADC decrease graded as <50%, 50% to 60%, 60% to 70%, and 70% to 80% of the contralateral value were determined by thresholding. Patients were categorized as normalizers (demonstrating ADC normalization in >5 mL tissue with initially decreased ADC) or nonnormalizers (demonstrating ADC normalization in <5 mL tissue).

Results—Fourteen patients (19.7%) were classified as normalizers. Eleven of 31 patients (35.5%) initially imaged <3 hours after stroke onset and 3 of 37 (7.5%) of those imaged 3 to 6 hours after onset were normalizers. ADC normalization occurred predominantly in the basal ganglia and white matter after thrombolytic therapy in patients with more distal vessel occlusions. All normalizers demonstrated at least partial tissue reperfusion. Tissue with more severe initial decrease in ADC was less likely to demonstrate normalization.

Conclusions—ADC normalization is not a rare event in acute stroke after tissue reperfusion. Brain tissue with initially decreased ADC, especially within 3 hours after stroke onset, may include “tissue at risk.” (Stroke. 2004;35:514-519.)

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

Multiparametric stroke imaging combining diffusion-weighted MRI (DWI) and perfusion-weighted MRI (PWI), MR angiography (MRA), and conventional MR sequences is increasingly used as the primary diagnostic imaging modality in major stroke centers.1–5 It was a widely accepted hypothesis among clinicians that lesions with diffusion slowing represent tissue prone to infarction. Increased use of DWI in acute stroke has led to observations of early diffusion normalization in lesions that initially show diffusion slowing. Such “renormalization” may be spontaneous or may be the result of thrombolytic therapy.6–8 Thus, acute slowing of diffusion is not necessarily an indicator of irreversible tissue damage. These reports challenge the concept that the PWI–DWI mismatch indicates the entire “tissue at risk of infarction.”

It is important to fully define the frequency and characteristics of DWI normalization. Recently, a 0.2% to 0.4% probability of apparent diffusion coefficient (ADC) reversal was reported in a patient group with heterogeneous diagnoses.9 There are limited data about the frequency and extent of persistent ADC normalizations in stroke patients,6,10 especially in patients with intravascular thrombolysis. This raises 2 questions: (1) How often does ADC normalization occur in acute stroke patients, and what are the clinical consequences? (2) Are there predictors of ADC normalization?

We studied the frequency, anatomical localization, MRI characteristics, and clinical data of patients who displayed ADC normalization in 68 stroke patients who were initially imaged at the hyperacute stage (mean, 2.8 hours). We sought to identify the clinical and imaging appearance of ADC normalization.

Patients and Methods

Patients

Patients with sudden onset of ischemic stroke in the anterior circulation who underwent a complete MRI protocol within 6 hours after stroke onset (mean ± SD, 2.8 ± 1.0 hours) and a follow-up MRI on days 1 and 5 to 8 were included in the analysis. Patients with lacunar stroke and intracranial hemorrhage were excluded. There were no limitations because of other MR findings, age, or severity of symptoms. Furthermore, patients were excluded for the following reasons: technical failure of the initial PWI study and missing follow-up (transfer to another hospital, instability of vital signs, and unknown treatment [randomized controlled therapeutic trial]).
MULTIPARAMETRIC MRI was performed immediately after clinical evaluation and before possible intravenous thrombolysis with tissue plasminogen activator. The National Institutes of Health Stroke Scale (NIHSS) score was assessed by a stroke neurologist at each imaging time point. Informed consent was obtained from all patients. The study was approved by the local ethics committee. Thirty of the patients were included in a previous study with a different focus.

**Imaging Methods**

MRI studies were performed on a 1.5-T clinical whole-body scanner (Magnetom Symphony/Sonata, Siemens) using a standard head coil. The measurements included an axial DWI sequence, a PWI sequence, an MRA, and in most cases a fluid-attenuated inversion recovery (FLAIR) sequence. Table time was 20 minutes in most cases. MRI sequence parameters were described recently.

**Postprocessing**

Postprocessing of the DWI and PWI image data was performed offline with custom-written software, including MGH-Image and SCAN developed by the Stroke Center at the University of California, Los Angeles. The ADC was determined from diffusion trace maps (time to the maximum of $S_I$ changes) were calculated. The Stejskal-Tanner equation was used to model the diffusion signal intensity decay, where $R_2^* = \ln[S_i(t)/S_0]/TE$, where $S_i(t)$ is the signal intensity at the time point $t$ after injection of the contrast agent, $S_0$ is the signal intensity without contrast agent, and $TE$ is the echo time. Principles of the indicator dilution theory for nondiffusible tracers were applied to the determined concentration-time curves. Time-to-peak (TTP) maps (time to the maximum of $S_i$ changes) were calculated. The volume with a perfusion abnormality was manually delineated as the area with a perfusion abnormality >2 seconds compared with the contralateral hemisphere.

The b=0 DWI images obtained at day 5 to 8 were used as T2-weighted (T2w) images for determination of final lesion volumes. During manual lesion delineation, FLAIR images from days 0 and 5 to 8 were available for comparison to exclude cerebrospinal fluid spaces and preexisting lesions. Furthermore, regions with hemorrhagic transformation or parenchymal hemorrhage, which could be identified on the T2*w PWI data, were included in the final lesion volume, so that false normalizations resulting from hemorrhagic transformation were excluded. Volumes were calculated using voxel count, voxel size, and interslice gap.

**Results**

Sixty-eight patients (19 women, 49 men; mean±SD age, 62±12 years) with sudden onset of ischemic stroke during

### TABLE 1. Characteristics of Patients With and Without ADC Normalization

<table>
<thead>
<tr>
<th></th>
<th>Norm</th>
<th></th>
<th>Progr</th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58.6</td>
<td>9.9</td>
<td>62.6</td>
<td>13.1</td>
<td>0.271</td>
</tr>
<tr>
<td>Time to initial MRI, h</td>
<td>2.7</td>
<td>1.0</td>
<td>3.0</td>
<td>0.8</td>
<td>0.247</td>
</tr>
<tr>
<td>NIHSS (day 0)</td>
<td>12.5</td>
<td>5.9</td>
<td>13.5</td>
<td>5.5</td>
<td>0.602</td>
</tr>
<tr>
<td>NIHSS (day 5–8)</td>
<td>2.9</td>
<td>3.4</td>
<td>6.5</td>
<td>6.9</td>
<td>0.189</td>
</tr>
<tr>
<td>Lesion volume ADC day 0, mL</td>
<td>36.9</td>
<td>35.2</td>
<td>44.9</td>
<td>46.8</td>
<td>0.847</td>
</tr>
<tr>
<td>Lesion volume TTP day 0, mL</td>
<td>98.9</td>
<td>58.0</td>
<td>232.4</td>
<td>121.0</td>
<td>0.000</td>
</tr>
<tr>
<td>Lesion volume T2 day 5–7, mL</td>
<td>19.3</td>
<td>14.9</td>
<td>68.9</td>
<td>68.2</td>
<td>0.001</td>
</tr>
<tr>
<td>T2 (day 5–7) – ADC (day 0), mL</td>
<td>−16.1</td>
<td>9.8</td>
<td>32.9</td>
<td>51.3</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Norm indicates normalization; Progr, no normalization.
the last 6 hours (2.8±0.8 hours; range, 1.5 to 5.2 hours) completed the follow-up until day 5 to 8.

Occlusion types were carotid T (n=12), proximal ICA and MCA (n=11), combined anterior cerebral artery and MCA (n=2), proximal MCA trunk (n=19), distal MCA trunk (n=7), MCA branch (n=16), and no vessel occlusion (n=1). Mean initial NIHSS was 13.3±5.3. Patients were treated conservatively (aspirin and low-molecular-weight heparin; n=19), with early hemicraniectomy (n=2), and by intravenous (n=24 within <3 hours, n=20 within 3 to 6 hours) or intra-arterial thrombolysis (n=3 within 3 to 6 hours).

Of the 68 patients, 14 (20.6%) showed a normalization of >5 mL (Figure 1). Mean±SD normalization volume was 16.1±9.8 mL. ADC normalization was time dependent. It was observed in 11 of 31 patients (35.5%) imaged within 3 hours after stroke onset but only in 3 of 37 patients (8.1%) imaged between 3 and 6 hours after stroke onset.

The initial total ADC lesion volumes (VolumeADC) were not significantly different between patients with and without ADC normalization (Table 1). ADC normalization was observed in white matter (n=10) and in the basal ganglia (always incomplete; n=4) (Figure 2).

Lesions volumes that showed normalization had the following composition with respect to ADC categories: 6% (<50% ADC), 16% (50% to 60% ADC), 29% (60% to 70% ADC), and 49% (70% to 80% ADC). In contrast, the lesions evolving to infarction were composed by 13%, 25%, 28%, and 35% of the different ADC categories, respectively (Figure 3b). The ratio of tissue volume evolving to normalization compared with infarction increased continuously with increasing ADC for each of the ranges (Figure 3a). Complete reperfusion was present in most of the patients with ADC normalization on MRI follow-up at day 1 (TIMI 3; n=9 of 14). The remaining patients that showed ADC normalization had at least partial reperfusion (TIMI 2; n=4 of 14). In 1 patient with ADC normalization, perfusion MRI results from day 1 could not be obtained because of a technical problem. In the group showing ADC normalization, the rate of complete reperfusion after 24 hours was significantly higher compared with patients without normalization (9 of 14 versus 9 of 54; P<0.05) (Figure 4).

The initial PWI volume and T2w lesion volume on day 5 to 8 were smaller (each P<0.001) in patients showing ADC normalization. Occlusion of MCA branches was the predominant occlusion type in patients with ADC normalization (7 of 14 versus 9 of 54) (Figure 4). There were no significant

TABLE 2. Demographics of Patients With ADC Normalization

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Sex</th>
<th>Time to MRI, H</th>
<th>Occlusion Type</th>
<th>Therapy</th>
<th>Recanalization at Day 1</th>
<th>NIHSS</th>
<th>Lesion Volume, mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Day 0</td>
<td>Day 5–8</td>
</tr>
<tr>
<td>1</td>
<td>42</td>
<td>M</td>
<td>2.5</td>
<td>MCA branch</td>
<td>IV</td>
<td>Complete</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>M</td>
<td>2.0</td>
<td>MCA branch</td>
<td>IV</td>
<td>Complete</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>62</td>
<td>M</td>
<td>2.0</td>
<td>MCA branch</td>
<td>IV</td>
<td>Complete</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>M</td>
<td>2.0</td>
<td>MCA trif</td>
<td>IV</td>
<td>Complete</td>
<td>15</td>
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<tr>
<td>5</td>
<td>43</td>
<td>F</td>
<td>3.5</td>
<td>MCA trunk</td>
<td>IA</td>
<td>Partial</td>
<td>21</td>
<td>12</td>
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<tr>
<td>6</td>
<td>52</td>
<td>M</td>
<td>2.8</td>
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<td>IV</td>
<td>Partial</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>M</td>
<td>4.7</td>
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<td>Partial</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>62</td>
<td>M</td>
<td>1.5</td>
<td>ICA and MCA</td>
<td>IV</td>
<td>Partial</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>9</td>
<td>63</td>
<td>M</td>
<td>4.3</td>
<td>MCA branch</td>
<td>IV</td>
<td>Unknown</td>
<td>16</td>
<td>4</td>
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<tr>
<td>10</td>
<td>75</td>
<td>F</td>
<td>2.8</td>
<td>MCA trunk</td>
<td>IV</td>
<td>Complete</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>11</td>
<td>45</td>
<td>M</td>
<td>3.5</td>
<td>ICA and MCA</td>
<td>IA</td>
<td>Complete</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>12</td>
<td>67</td>
<td>M</td>
<td>2.5</td>
<td>ICA and MCA</td>
<td>IV</td>
<td>Complete</td>
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<tr>
<td>13</td>
<td>62</td>
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<tr>
<td>14</td>
<td>69</td>
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<td>Complete</td>
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<td>0</td>
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<tr>
<td>Mean</td>
<td>58.6</td>
<td>2.7</td>
<td></td>
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<td></td>
<td></td>
<td>12.5</td>
<td>2.9</td>
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<tr>
<td>SD</td>
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<td>0.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.8</td>
<td>3.1</td>
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</tbody>
</table>

*IV indicates systemic thrombolysis; IA, local thrombolysis.
differences in lateralization, sex, and age. For mean values and further comparisons, see Table 1 and Figure 4.

Discussion

Stroke patients have a considerable volume of tissue at risk of infarction even between 3 and 6 hours after stroke onset.\textsuperscript{3,4,5} Patient selection based on the presence of a mismatch between DWI and PWI might therefore justify extension of the time window for thrombolysis beyond 3 hours after stroke onset.\textsuperscript{4,5,6} Former animal research\textsuperscript{7,8} and recent clinical studies\textsuperscript{9,10} reported on the potential normalization of diffusion lesions. These reports suggest that lesions identified on the acute DWI study do not necessarily indicate irreversible tissue damage. Thus, threatened but potentially salvageable tissue (tissue at risk) includes not only tissue with abnormal perfusion and normal diffusion but also potentially some tissue with abnormal diffusion. We studied the frequency and characteristics of lesions undergoing early normalization of initially decreased ADC values within 6 hours after stroke onset, a time interval relevant for decisions concerning thrombolysis therapy in acute stroke patients.\textsuperscript{11}

ADC normalization occurred in \approx20\% of the acute stroke patients in our sample and therefore was not a rare event, especially if patients were studied at a very early time point (mean, 2.8 hours) (Figure 1). Several recent articles report a lower frequency of normalization than we found.\textsuperscript{10,19,20} We believe that the lower frequency of normalization in these reports is due to the later initial imaging time point (<12 hours)\textsuperscript{19} and to the absence of treatment with thrombolytics.\textsuperscript{10,20} Our patients had comparatively proximal vessel occlusions and severe stroke symptoms and arrived in our center early with the option to receive thrombolytic therapy. Conclusions from our results cannot be easily transferred to all stroke patients.

All normalizers demonstrated at least partial tissue reperfusion in the scan performed on the first day after stroke onset, as presumptively demonstrated by normal or accelerated TTP in a region with previously decreased ADC (Figure 4). Thus, reperfusion was a prerequisite for ADC normalization in our study. However, information about time point and sufficiency of reperfusion cannot be derived from TTP maps on day 1. Patients with ADC normalization displayed more

Figure 3. In patients with ADC normalization, ADC lesion volumes were graded by thresholding into ADC decreases <50\%, 50\% to 60\%, 60\% to 70\%, and 70\% to 80\% of contralateral mean hemispherical value. Each volume was subdivided into categories of later infarction (progr) and ADC normalization (norm). a, Composition of initial lesion volumes in respect to graded ADC decrease in volumes of later infarction or ADC normalization. b, Ratio of tissue volume showing normalization vs infarction increased in ranges with increasing ADC.

Figure 4. Relations and absolute numbers for patients showing ADC normalization (norm) or absent normalization (progr) for (a) reperfusion after 24 hours, (b) site of vessel occlusion, (c) occlusion type, and (d) time of initial MRI.
distal vessel occlusions, consistent with the known higher recanalization rates for distal vessel occlusions compared with proximal occlusions.21,22

In patients showing partial normalization, the proportion of tissue volume showing normalization compared with infarction decreased when ADC was initially more severely decreased (Figure 3). This finding supports previous reports suggesting that regions with ADC normalization have initially less severe ADC decreases in individual patients.8,23 On the other hand, we observed ADC normalization of tissue with an initial ADC decrease of <50% in individual patients. Thus, severe initial ADC decreases do not uniformly predict infarction.7,24

Two regions of ADC normalization were observed: white matter (Figure 2a) and parts of the basal ganglia (Figure 2b). It was somewhat surprising to detect a partial ADC normalization in the basal ganglia because the opposite has been shown in experimental work. The caudate putamen revealed a more pronounced ADC decrease (and tissue damage) than the substantia nigra and thalamus25 or the cortex.26 Although these reports argue against the recovery of deep brain structures, a recent study reported on ADC normalizations in subcortical gray matter ischemia.27 We believe that our observation can be explained by the complex flow patterns in the basal ganglia.28 We are not able to resolve this puzzle because of the finite spatial and temporal resolution of our methods. However, we occasionally found an ADC decrease without TTP delay, suggesting that reperfusion had occurred by the time of the initial study (Figure 2).

Patients with ADC normalization showed a tendency toward better clinical outcome in our study. However, the absolute improvement in NIHSS was not significantly different from that in patients without normalization in our sample. Although the mean tissue volume that displayed normalization was relatively small (mean, 16 mL; Figure 1), it is possible that the better clinical outcome in the group showing normalization was the result of salvaging functionally eloquent brain regions.

This perspective assumes that ADC normalization is an indicator of tissue salvage. However, it is not known whether the absence of a T2w lesion in follow-up MRI is an accurate indicator of functional tissue, given that selective neuronal loss has been observed in regions of normal-appearing T2w signal in postischemic MRI scans.29,30 Hence, it is not known whether the more favorable clinical outcome in the group showing ADC normalization is due to the salvage of small tissue areas, to some indirect benefit of vessel recanalization, or to the initially less extensive perfusion abnormalities found in this group.

One important question that arises from our study is whether thrombolysis should be attempted in patients who fail to show a PWI–DWI mismatch. The mismatch concept is supported by our data because patients with infarct growth had significantly larger mismatch volumes, indicating a larger tissue at risk (Table 1). On the other hand, one fifth of our patients showed a decrease in final lesion size compared with the initial DWI lesion size. This ADC normalization phenomenon seems to be time dependent: ADC normalizations occurred in 11 of 31 patients (35.5%) studied <3 hours after symptom onset but in only 3 of 37 patients (8.1%) studied within 3 to 6 hours after symptom onset. Based on our findings, the tissue at risk as target of thrombolysis therapy might be extended toward the DWI lesion at least within 3 hours after stroke onset. Consequently, at least within <3 hours, the absence of a PWI–DWI mismatch does not imply the absence of tissue at risk. In some patients, there can be some tissue that might profit from therapeutic reperfusion. The possible benefit of thrombolysis in these patients without mismatch needs further investigation.

Conclusions

ADC normalization in stroke is not rare when MR imaging is performed in the hyperacute period. It occurs predominantly in the basal ganglia and white matter and in patients with more distal vessel occlusions. Early reperfusion is a prerequisite for ADC normalization. Tissue prone to ADC normalization is characterized by less severe initial ADC decreases. Tissue displaying a PWI–DWI mismatch remains the major target of thrombolytic therapy; however, the tissue at risk of infarction might also include parts of the DWI lesion, especially within 3 hours after stroke onset.

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References


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