Failure to Demonstrate Peri-Infarct Depolarizations by Repetitive MR Diffusion Imaging in Acute Human Stroke

Tobias Back, MD; Jochen G. Hirsch, PhD; Kristina Szabo, MD; Achim Gass, MD

Background and Purpose—Peri-infarct depolarizations (PIDs) have been demonstrated with diffusion-weighted MRI (DWI) in experimental stroke and are regarded as an important mechanism of ischemic injury. We tested the hypothesis that PIDs are of relevance for the early enlargement of human brain infarcts.

Methods—Ten stroke patients were investigated by repetitive imaging of the apparent diffusion coefficient (ADC) in the acute phase (7 patients) or subacute phase (3 patients) of developing cortical infarction. In each patient, 20 ADC maps were obtained from serially measured echo-planar DWI (interval of 45 seconds). Data analysis focused on the potential spatial and temporal ADC changes, including structured qualitative analysis, calculation of subtraction images, serial analysis of regions of interest positioned in the infarct core and border, and calculation of hemispheric lesion areas, depending on various ADC thresholds ranging between 0 and 800 μm²/s.

Results—Data analysis was unable to disclose any time-dependent changes in ADC that would resemble PID. In ischemic regions, the ADC reduction significantly progressed from the infarct border (555±96 μm²/s) to the infarct core (431±104 μm²/s, P<0.01).

Conclusions—By using an MRI protocol with high temporal resolution and elaborated postprocessing, we were unable to demonstrate a pattern of diffusion changes that would be indicative of PID in human stroke. Experimental infarction and human stroke may differ in the detectability of PID. (Stroke. 2000;31:2901-2906.)

Key Words: magnetic resonance imaging, diffusion-weighted spreading cortical depression stroke

The development of diffusion- and perfusion-weighted MRI has provided new insights into the evolution of focal cerebral ischemia in humans and in animal models of stroke.1-4 Serial diffusion-weighted imaging (DWI) has repeatedly demonstrated the enlargement of human cerebral ischemic lesions during the initial days after symptom onset.5-8 Several mechanisms may contribute to this phenomenon: vasogenic swelling of the initial lesion is usually observed, but recruitment of new tissue may also be involved in infarct growth. It has been suggested that subsequent infarct enlargement can be predicted by the initial mismatch between the perfusion deficit (larger) and the lesion size in DWI (smaller).5,7,9

In experimental stroke, Gyngell et al4 have shown by repeated DWI that regions with disturbed diffusion increased during the first 6 hours after middle cerebral artery (MCA) occlusion. The simultaneous measurements of 1H spectra and electrophysiological monitoring disclosed that infarct growth is promoted by spreading depression–like events known as peri-infarct depolarizations (PIDs), which lead to transient increases in the lactate signal (1H spectra),10 negativation of the direct current potential, and stepwise enlargement of the diffusion lesion.4,11 The propagation pattern of PID was studied by repetitive MR diffusion mapping,12 which demonstrated that depolarizations can be visualized by the transient reduction of the apparent diffusion coefficient (ADC), evolving from the infarct border and traveling with a speed of ≈3.5 mm/min over the ipsilateral cortex—a pattern that exactly resembles the electrophysiological changes seen in cortical spreading depression.13 The stimulation of the ischemic infarct border by local application of potassium, thereby inducing waves of depolarizations, has been shown to substantially increase subsequent ischemic injury.14,15 There is strong experimental evidence that PID contribute to infarct growth by means of their high metabolic impact14 (for review, see Back et al16).

At present, there is uncertainty whether this important mechanism of ischemic injury can be detected in stroke patients and should be a target of pharmacological intervention. To document diffusion changes that might follow a pattern known from spreading depression, we monitored early infarct evolution with a dedicated MRI protocol, using rapid repetitive diffusion MRI, in patients presenting with acute hemispheric stroke. Data analysis focused on potential signal changes in the infarct border or the diffusion-perfusion mismatch regions, which are prone to further lesion enlargement over time.
Subjects and Methods

Patients and Controls

Three healthy volunteers and 10 patients in the acute or subacute phase of stroke evolution were investigated prospectively. In all patients, there was cortical involvement in the MCA or anterior cerebral artery (ACA) territories (Table 1). Hemorrhage had been excluded by a cranial CT scan. The suspected clinical diagnosis of MCA and/or ACA occlusion was confirmed by ultrasound and MRI. The severity of the clinical deficit was assessed by the NIH Stroke Scale 17 and Scandinavian Stroke Scale28 scores at the time of MRI. Informed consent was obtained from all patients in writing before MRI. The study was approved by the local ethics committee. For clinical data, see Table 1.

MRI Techniques

MRI was performed on a 1.5-T MR System (Magnetom Vision, Siemens) with resonant echo-planar hardware. A standardized protocol was used: (1) Transverse, coronal, and sagittal localizing sequences followed by transverse oblique contiguous images (slice thickness 5 mm) aligned with the inferior borders of the corpus callosum (sequences 2 to 5). (2) Proton density- and T2-weighted images (turbo spin echo, repetition time/echo times 1 and 2 [TR/TE1/TE2] 2620 ms/14 ms/85 ms; field of view [FOV] 180×240 mm2; matrix 192×256). (3) T1-weighted images (spin echo, TR/TE 530 ms/12 ms). (4) MR angiography (fast, low-angle shot [FLASH]-3D: TR/TE/α, 35 ms/7.2 ms/20°; matrix 200×512; performed in 4 of 10 patients). (5) Similar to the methods applied in experimental MRI studies of spreading depression,19,20 repetitive, strongly DW images measured in 10 stroke patients were inspected for spiking and noncorrectable motion artifacts. ADC maps were calculated on a pixel-to-pixel basis by a linear least-squares fit after logarithmic averaging of the direction-dependent DW images.6 Perfusion maps were measured by using a computerized 2D matching procedure compensating for in-plane motion artifacts and eddy current distortions21 after all DW images were inspected for spiking and noncorrectable motion artifact. ADC maps were calculated on a pixel-to-pixel basis by a linear least-squares fit after averaging of the direction-dependent DW images. ADC subtraction images were calculated by subtracting the actual image (2 to 20) from the first image. Twenty repetitive ADC maps and 19 subtraction ADC images were used per patient for a structural visual analysis that was performed by 3 readers independently (T.B., J.G.H., and A.G.). A serial analysis was performed of regions of interest (ROIs; 3×4 pixel) positioned in the infarct core, the infarct border, and contralateral brain regions, and calculation of hemispheric lesion areas (HLAs), depending on various ADC thresholds ranging between 0 and 400, 500, 600, 700, or 800 μm2/s. To assess the hemodynamic alterations and confirm the ROI position, parameter maps of the contrast bolus passage were used (time-to-peak map; ie, the intensity of each pixel is related to the relative position of the peak of the bolus-passage curve).

For statistical analysis of repetitive ADC or HLA measurements, respectively, the paired Wilcoxon test for repeated measures was used. Significant changes in ADC or HLA, respectively, were assumed if the Wilcoxon test revealed significant alterations of ADC or HLA in at least 3 consecutive measurements (because the duration of peri-infarct depolarizations was determined as ≥2.5 minutes in animal studies19,22 ). The different ROIs (cortex, striatum, infarct core, etc) were tested by the Student t test. The variance of ADC values determined in different ROIs was tested by the F test. P<0.01 was accepted as significant if not stated otherwise.

Results

The median latency between onset of stroke and the MR investigation amounted to 9.7 hours. Repetitive measurements of ADC in normal control subjects showed very stable measurement conditions, with a range of ADC values in the 10% range would be identified by the data postprocessing strategies described. Visual qualitative analysis of repetitive, strongly DW images measured in 10 stroke patients as well as the entire postprocessing strategies did not disclose any time-dependent changes in local ADC (Figures 1 and 2). Patient 4 was excluded from data analysis because of severe motion artifacts. We were not able to detect alterations in ADC, which would resemble spreading depression, as known from animal studies. The ADC values determined in various ROIs are presented in Table 2. As an example, the positioning of ROIs is shown in Figure 3. ROIs were placed in the infarct center, the inner and outer infarct borderzones,

TABLE 1. Clinical Data of Patients Examined by Serial MR DWI

<table>
<thead>
<tr>
<th>Patient No./Age, y/Sex</th>
<th>Ischemic Territory</th>
<th>Lesion Location</th>
<th>Latency Symptom Onset to MRI, h</th>
<th>NIH Stroke Scale (0–36 points)</th>
<th>Scandinavian Stroke Scale (58–0 points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/40/M 75/70/M</td>
<td>MCA R frontal</td>
<td>11.5, 11</td>
<td>41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/63/M 3/56/F</td>
<td>MCA L frontotemporal</td>
<td>6, 20</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/70/M 5/74/M</td>
<td>ACA R frontoparietal</td>
<td>13, 29</td>
<td>45, 43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/41/F 7/77/F</td>
<td>MCA R striatum</td>
<td>50, 114</td>
<td>4, 54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8/58/M 9/70/M</td>
<td>MCA+ACA R parietal, insular, and basal ganglia</td>
<td>8, 5, 2.5</td>
<td>13, 5, 21</td>
<td>28, 38, 4</td>
<td>4, 38, 4</td>
</tr>
<tr>
<td>10/47/F</td>
<td>MCA (bilateral) R frontal and L frontoparietal</td>
<td>2, 8</td>
<td>48</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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the contralateral cortex, striatum, and white matter (Figure 3). The distribution of ADC in the infarcted hemisphere showed that there was a gradient of ADC reduction from the infarct periphery toward the infarct core regions, where ADC was lowest and amounted to 57% of contralateral cortex (Table 2).

The same pattern became obvious when various ADC thresholds were applied depicting only pixels within a certain range of ADC (Figure 4). The time course of ADC values as determined in ROIs positioned in the infarct region, the diffusion-perfusion mismatch area, or the contralateral hemisphere did not disclose any significant changes during the measurement period (Figure 5). Also, the 20 consecutive measurements of HLAs depicting certain ADC ranges of the ischemic lesions, as stated above, did not reveal significant changes over time (Figure 6). However, the serial ADC values measured within the ischemic regions (infarct core and inner and outer borderzones) varied over time in a significantly greater range compared with the contralateral nonischemic brain regions (F test, \( P < 0.01 \)).

In 6 of 10 patients, the perfusion deficit was visualized by bolus-tracking images. The area with increased time-to-peak matched well the region with disturbed diffusion (\( n = 3 \)) or contained a larger territory (\( n = 3 \)) as an indication of the hemodynamic compromise beyond the diffusion lesions. In the latter 3 patients, the area with reduced ADC encompassed 1815 mm\(^2\) and the perfusion deficit 2648 mm\(^2\), respectively (mean values, determined at midinfarct level). ADC as measured in those mismatch regions amounted to 798 ± 37 \( \mu \text{m}^2/\text{s} \) and did not differ from contralateral values (807 ± 33 \( \mu \text{m}^2/\text{s} \)). MR angiography was able to demonstrate proximal MCA occlusion (M1 segment) in 2 of 5 cases with extended large MCA territory infarction. MCA branch occlusion lead to a rarefaction of MCA.

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### Table 2. ADC Values in Various Brain ROIs Measured in Acute Stroke Patients and Healthy Control Subjects

<table>
<thead>
<tr>
<th>ROI</th>
<th>Patients (n=9)</th>
<th>Healthy Controls (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonischemic hemisphere</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortex</td>
<td>763±42</td>
<td>746±53</td>
</tr>
<tr>
<td>Striatum</td>
<td>754±39</td>
<td>732±39</td>
</tr>
<tr>
<td>White matter</td>
<td>756±49</td>
<td>788±45</td>
</tr>
<tr>
<td>Ischemic hemisphere</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infarct core region</td>
<td>431±104*</td>
<td>...</td>
</tr>
<tr>
<td>Inner infarct border</td>
<td>451±70*</td>
<td>...</td>
</tr>
<tr>
<td>Outer infarct border</td>
<td>555±96†</td>
<td>...</td>
</tr>
</tbody>
</table>

Values were obtained by ROI analysis using 20 consecutive measurements in 1 to 3 slices per patient or healthy control. ROI size amounted to 3×4 pixel.

*Significantly different from values of outer infarct border, cortex, striatum, and white matter, \( P < 0.001 \); †significantly different from values of cortex, striatum, and white matter, \( P < 0.001 \).
branching or, alternatively, could not be visualized due to the limited spatial resolution.

Discussion

In animal models of focal cerebral ischemia, repetitive imaging of DW or ADC images has been able to demonstrate a typical pattern of spreading alterations in tissue diffusion which paralleled electrophysiological measurements confirming the occurrence of spreading depression of electrical activity.4,10,19,20 Those spreading depression–like peri-infarct depolarizations have been observed in cat cortex up to 16 hours after MCA occlusion (ie, the end point of experiments).23,24 We have chosen a very similar MRI protocol to investigate patients presenting with acute supratentorial stroke. Attention was paid (1) to minimize the latency between symptom onset and MRI measurements (which was a median of 9.7 hours in our series) and (2) to apply a MR technique that would be sufficient with regard to the stability of measurements and the spatial/temporal resolution to detect such reversible changes in ADC traveling over the cortical surface. However, we were unable to demonstrate ADC alterations which, in their spatial and temporal patterns, would resemble PIDs. By using control studies and computer simulations, we ensured that ADC changes in the 10% range would be detectable by the postprocessing strategies used. Thus, technical limitations are unlikely to explain the negative results.

The ADC values obtained in the ischemic regions under investigation are in good agreement with the literature.25–27 The ROI analysis clearly showed a gradient of ADC reduction, with progressively lower ADC values moving from the infarct periphery toward the infarct core (Table 2, Figure 4). This observation supports the view that the ischemia-induced early change in ADC is a blood flow–dependent event which reflects the severity (and duration) of the perfusion deficit,28,29 but partial volume effects at the edges of the lesions may partly account for this finding. It has been shown that the mismatch between the perfusion deficit (larger) and the diffusion lesion (smaller) may indicate the tissue at risk of undergoing infarction and potential infarct enlargement.5–7,27 In our series, half of the patients examined by bolus-tracking perfusion images showed this mismatch pattern and, therefore, could be expected to experience infarct growth over time. Even patients with a mismatch did not show evidence of significant ADC changes over the 15-minute observation period. ADC values within the mismatch regions remained normal. The fact that ADC values within ischemic regions varied in a significantly greater range over time than those observed on the contralateral side indicates an increased temporal (and spatial) heterogeneity within the diffusion lesion. Whether this is due to partial tissue depolarization without a
it may well be that we have missed transient depolarizations which last 2 to 5 minutes, because the time period covered by repetitive ADC imaging amounted to 15 minutes per patient. Given the assumption that 1 depolarization would occur per 2 hours, the statistical probability to detect this phenomenon is just 1 per 8 patients. Our cohort consisted of 10 patients, but only 7 of them had been investigated within 24 hours after onset of symptoms. Therefore, an extended study that includes a higher number of patients is clearly desirable to substantiate our findings. Second, the cortical architecture is much more complex in humans, which also may affect the propagation pattern of tissue depolarization. We performed ADC measurements in 3 transverse planes through the infarct center so that depolarizations traveling distant from the planes under investigation would have been missed. Yet, it appears that peri-infarct depolarizations are much rarer in human stroke (if they occur at all) compared with animal studies.

(3) PIDs do occur in human stroke, but they cannot be detected by diffusion MRI. We do not know whether tissue depolarization in the human cortex would alter ADC in the magnitude known from animal studies. Recent findings made by Moskowitz and coworkers\(^{37}\) in the cortex of a migraine patient when using blood oxygen level–dependent (BOLD) MRI are also interesting in this respect. During the migraine aura, they observed a spreading suppression of functional (visual) activation traveling over the occipital cortex at \( \approx 3.5 \text{ mm/min} \), ie, a depression of the normal hemodynamic response after cortical activation.\(^{37}\) Simultaneous measurements of the ADC did not show significant alterations (oral communication, M.A. Moskowitz, MD, Charlestown, Mass, 1999). This finding is in line with a recent study that used perfusion- and diffusion-weighted MRI in migraine patients demonstrating cortical “spreading hypoperfusion” without accompanying changes in tissue diffusion during the aura.\(^{38}\)

We favor the view that the lack of ADC changes possibly indicates a lower level of spreading depression–associated electrical and/or hemodynamic compromise in human brain. Alternatively, the blood flow threshold for altering tissue water diffusion may be lower in humans compared with that in animal studies of ischemia (ie, 0.41 mL·g\(^{-1}\)·min\(^{-1}\)). This may also explain why we were unable to detect PID with ADC imaging but BOLD MRI may be appropriate to detect an equivalent of the spreading depression observed in experimental studies. It has been shown that the pharmacological inhibition of ischemic depolarizations reduces infarct volumes in animal models of stroke.\(^{34,40–42}\) It appears, therefore, of high importance to extend MRI investigations of the occurrence and characteristics of peri-infarct depolarizations in human stroke.

Acknowledgments

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