Is There an Apparent Diffusion Coefficient Threshold in Predicting Tissue Viability in Hyperacute Stroke?

Catherine Oppenheim, MD; Cécile Grandin, MD, PhD; Yves Samson, MD, Anne Smith, MD, PhD; Thierry Duprez, MD; Claude Marsault, MD; Guy Cosnard, MD

Background and Purpose—Rapid and precise identification of the penumbra is important for decision-making in acute stroke. We sought to determine whether an early and moderate decrease in the apparent diffusion coefficient (ADC) may help to identify, within the diffusion/perfusion (DWI/PWI) mismatch, those areas that will eventually evolve toward infarction.

Methods—We reviewed 48 patients not treated by thrombolytics who had a DWI/PWI within 6 hours after onset, with infarct evolution documented by follow-up magnetic resonance on days 2 to 4. We calculated absolute values for ADC and the ADC ratio (ADCr) in (1) the initial DWI hypersignal; (2) the final volume of the infarct, ie, the follow-up fluid-attenuated inversion recovery abnormalities; (3) the infarct growth (IGR) area; and (4) the oligemic area (OLI) that remained viable despite initial hemodynamic disturbance. We tested the value of the ADC to predict tissue outcome by using discriminant analysis.

Results—ADC values were marginally but significantly decreased in the IGR area (ADC 782±82×10^{-6} mm^2/s, ADCr 0.94±0.08) compared with mirror values (P=0.01) and with OLI (ADC 823±41×10^{-6} mm^2/s, ADCr 0.99±0.07; P=0.001). Of all quantitative DWI and PWI parameters, the ADCr best discriminated between IGR and OLI (F_{1,50}=13.6, cutoff=0.97, 64% sensitivity, 92% specificity) and between the final volume of infarct and OLI (F_{1,83}=219, cutoff=0.91, 91% sensitivity, 100% specificity).

Conclusions—A simple approach based on ADC alone may allow the identification of tissue at risk of infarction in acute-stroke patients. (Stroke. 2001;32:2486-2491.)

Key Words: diffusion ■ magnetic resonance imaging ■ penumbra ■ stroke

The ischemic penumbra is defined as functionally impaired but salvageable ischemic brain tissue surrounding an irreversibly damaged core and is the target of most recent treatments for acute stroke. The penumbra changes rapidly with time and differs from patient to patient. Therefore, rapid and precise identification of the penumbra is of considerable interest for decision-making in acute-stroke treatment. For and precise identification of the penumbra is of considerable importance for decision-making in acute-stroke treatment.2–5 For this purpose, magnetic resonance angiographic data and diffusion- and perfusion-weighted MRI (DWI and PWI, respectively) are regarded as the most suitable tools in a clinical setting.6 The so-called PWI/DWI mismatch, ie, the difference between a large abnormal area on PWI and a smaller bright area on DWI, is currently the most used index of the ischemic penumbra.3,9–12 However, there is strong evidence that the PWI/DWI mismatch is an imperfect approximation of the true ischemic penumbra.10,13,14 First, qualitative indices are often used to determine the size of PWI abnormalities,5,9,12 because PWI-based calculations of quantitative cerebral blood flow (CBF) values are time-consuming...
occur in reversible ischemic injury.  

On the basis of these considerations, we tried to ascertain whether ADC thresholds within the first 6 hours after stroke onset could help to predict infarct growth and final infarct size, and we compared the accuracy of the prediction based on ADC thresholds with that based on PWI quantitative measurements.

Subjects and Methods

Patients

Among 139 consecutive patients who had an MRI for suspected acute stroke, we selected all patients who met the following criteria: (1) acute cerebral infarct of the anterior circulation confirmed on follow-up MRI obtained within 4 days after stroke onset; (2) initial MRI obtained within 6 hours after stroke onset, including at least fluid-attenuated inversion recovery (FLAIR), DWI, and PWI; and (3) no thrombolytic or experimental neuroprotective agent. Forty-eight patients met these criteria (29 men, 19 women; mean age 69 ± 13 years, range 26 to 91 years). The mean European stroke scale on admission was 58 ± 25 (range 9 to 96). All patients received 300 mg/d acetylsalicylic acid.

MRI Protocol

At the acute phase (mean delay between MRI and symptom onset 3.2 ± 1.2 hours, range 1.4 to 6 hours), the MRI (1.5T Signa Echospeed scanner, GE Medical System) included a FLAIR, DWI, bolus tracking PWI, and magnetic resonance angiogram of the Willis circle. A follow-up MRI included a FLAIR sequence (mean 36 ± 18 hours, range 24 to 96 hours after the first examination). All images were acquired in the anterior commissure–posterior commissure plane with 5-mm slice thickness, 0.5-mm gap, 24 × 24-cm² field of view, and 24 slices enabling whole brain coverage. The acquisition parameters of the fast FLAIR sequence were as follows: repetition time (TR)/echo time (TE)/inversion time (TI) 10 002/148/2200 ms, matrix 256 × 160. A T2-weighted baseline acquisition (b = 0 s/mm²) and diffusion-weighted images were acquired with a single-shot, echo-planar, spin-echo sequence (TR/TE 4500/95 ms, matrix 96 × 64). The diffusion trace images were calculated from 3 diffusion-weighted acquisitions with the diffusion gradients sequentially applied along each of the 3 orthogonal axes and with b = 1000 s/mm², δ = 32 ms, Δ = 39 ms, and gradient amplitude = 22 mT/m. The perfusion-weighted images were acquired by using the dynamic first-pass bolus-tracking method and a single-shot, echo-planar, gradient-echo sequence (TR/TE 2300/30 ms, matrix 96 × 64). A dose of 0.1 mmol/kg Gd-DTPA (Magnevist, Schering AG) was injected at a rate of 10 cm³/s into a peripheral vein through an 18-gauge catheter by using a magnetic resonance compatible power injector (Spectris, Medrad Inc), followed by a 30-cm³ saline flush. The sequence duration was 46 seconds.

Data Processing

All images were processed on an independent workstation (Sun Ultra 1/200, Sun Microsystems) by using custom software (Research Systems Inc).  

Regions of Interest

All images were spatially coregistered to the first acquisition of the perfusion-weighted sequence to superimpose the regions of interest (ROIs) delineated on each type of image. The concentration-versus-time curves were fitted to a γ variate function to create parametric maps. The apparent mean transit time (apMTT) map, defined as the first moment of the measured tissue curve, was the only parametric perfusion map used to draw ROIs. Two neuroradiologists, blinded to other images and clinical symptoms, independently drew 3D ROIs by manual contouring on each slice: (1) the abnormal bright area on the initial DWI ROI was the volume of initial DWI abnormalities and was considered to represent the ischemic core; (2) the abnormal bright area on the initial apMTT map, and (3) the abnormal bright area on the initial ADC map. The regions of interest retrospectively divided into an IGR area and an OLI (panel E) and copied onto the initial ADC map (panel D). ADC values were 664, 801, 695, and 842 × 10⁻⁶ mm²/s in DWI, IGR, INFfinal, and OLI, respectively. In this case, absolute ADC values are below the defined thresholds for IGR (803 × 10⁻⁶ mm²/s) and INFfinal (748 × 10⁻⁶ mm²/s) and above these thresholds for OLI ROIs.
initially it was normal on DWI but evolved to infarction on follow-up FLAIR images; and (4) the oligemic area (OLI) was the apMTT minus the INFfinal ROI and corresponded to the part of the mismatch area that remained viable (see Figure). The DWI, INFsub, IGR, and OLI volumes were calculated as the sum of the area of the ROIs on each slice multiplied by the slice thickness plus the interslice gap. Mirror symmetrical regions were called mirror DWI, mirror IGR, and mirror OLI.

**Quantitative Diffusion and Perfusion Measurements**

ADC maps were created from 2-point analysis on a pixel basis by use of Func tool 1.9 software. ADC values were thresholded at 1200 mm²/s to minimize partial volume effect with the cerebrospinal fluid, and the previously defined ROIs were copied onto the ADC maps. As suggested by others,7,15,26,27 ADC ratios (ADCr) were obtained to minimize the influence of the cerebrospinal fluid. They were calculated by dividing each ADC value measured in the infarcted hemisphere by the symmetrical ROI. Quantitative measurements of CBF, cerebral blood volume (CBV), and mean transit time (MTT), obtained after extraction of the arterial input function, have been reported previously.14 Interobserver reliability for ADC values for quantitative volume and perfusion measurements using the same methodology has been reported elsewhere. Interobserver correlation for quantitative volume and perfusion measurements using the same methodology has been reported elsewhere.14 Excellent interobserver correlation for quantitative volume and perfusion measurements using the same methodology has been reported elsewhere.14

**Results**

The volume of the lesion increased from 37±8 cm³ (initial DWI ROI) to 44±6 cm³ (INFsub ROI) in the whole population. This corresponded to different changes in 3 subgroups of patients. In 14 patients (group 1), there was an infarct growth, and the mean volume increase reached 26±23 cm³ (range 2.1 to 70 cm³). In 29 patients (group 2), there was no infarct growth (0.3±1.4 cm³). In the remaining 5 patients (group 3), there was a slight volume decrease (4.7±2.5 cm³).

An area of prolonged apMTT was observed in all but 2 patients, and as expected, its volume (114±86 cm³) was much larger than that of initial DWI and final FLAIR abnormality. Accordingly, a PWI/DWI mismatch (mean volume 92±64 cm³) was observed in 38 (79%) of 48 patients, including all patients in group 1, 20 of 29 patients in group 2, and 4 of 5 patients in group 3. A middle cerebral artery or carotid T occlusion was observed in 9 of 14 patients in group 1, in 7 of 29 patients in group 2, and in 2 of 5 patients in group 3.

**ADC Values in the Different ROIs**

<table>
<thead>
<tr>
<th>ROI</th>
<th>Mean±SD</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADCDWI</td>
<td>661±68</td>
<td>664</td>
<td>513–789</td>
</tr>
<tr>
<td>ADCIGR</td>
<td>782±82</td>
<td>830</td>
<td>523–856</td>
</tr>
<tr>
<td>ADCOLI</td>
<td>823±41</td>
<td>829</td>
<td>715–903</td>
</tr>
<tr>
<td>ADCConsistent</td>
<td>821±44</td>
<td>819</td>
<td>719–910</td>
</tr>
<tr>
<td>ADCcontrolateral</td>
<td>0.8±0.7</td>
<td>0.8</td>
<td>0.66–0.96</td>
</tr>
<tr>
<td>ADCratio</td>
<td>0.94±0.08</td>
<td>0.95</td>
<td>0.69–1.02</td>
</tr>
<tr>
<td>ADCratio</td>
<td>0.99±0.02</td>
<td>0.99</td>
<td>0.92–1.04</td>
</tr>
</tbody>
</table>

ADC ratio and absolute ADC values in DWI (ie, initial DWI hypersignal, n=47), IGR (infarct growth region, n=14), OLI (oligemic area that remained viable despite initial hemodynamic disturbance, n=38), and pooled contralateral (n=99) ROIs are shown.

**Infarct Growth Subgroups**

As stated above, 14 patients had an apparent infarct growth (group 1), 29 had a stable lesion (group 2), and the remaining 5 had a partially reversible lesion (group 3). The ADC values were significantly different in the DWI region, being lower in group 1 (630±68×10⁻⁶ mm²/s) than in group 2 (667±59×10⁻⁶ mm²/s) and group 3 (725±40×10⁻⁶ mm²/s) (P=0.047, F₁₂₄=3.28). The same trend (P=0.08) was observed for ADCr. Conversely, ADC values were similar in the OLI areas of the 3 groups (group 1, 835±45×10⁻⁶ mm²/s; group 2, 814±38×10⁻⁶ mm²/s; and group 3, 832±45×10⁻⁶ mm²/s).

**Discriminant Analysis**

The IGR versus OLI discriminant analysis (Table 2) showed that the fate of the mismatch region was predicted as accurately by ADC measurements as by CBF or CBV.
When a therapeutic decision is made regarding an acute ischemic stroke, it is important to know whether a DWI abnormality detected during the therapeutic window will tend to increase spontaneously during the next few days. This requires an accurate and immediate distinction of the already infarcted and still-at-risk ischemic tissue. In this field, research has been dominated by work on the PWI/DWI mismatch. Precise CBF thresholds for penumbra have been found, but tissue prognosis of the penumbra remains uncertain. The PWI/DWI mismatch region may exceed the true penumbral area and is usually much larger than the final size of the infarct. These limitations led us to investigate the value of an ADC quantitative assessment of early tissue changes, especially in the mismatch area. We found that ADC thresholds may help to predict infarct growth within the mismatch area and, even more accurately, the final size of the infarct.

**Discussion**

**Table 2. Prediction of IGR vs OLI**

<table>
<thead>
<tr>
<th>Cutoff Value</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>F*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC</td>
<td>803×10⁻⁶ mm²/s</td>
<td>74</td>
<td>5.6</td>
<td>0.02</td>
</tr>
<tr>
<td>ADCr</td>
<td>0.97</td>
<td>92</td>
<td>13.6</td>
<td>0.0006</td>
</tr>
<tr>
<td>CBF</td>
<td>38 cm³/min per 100 g</td>
<td>62</td>
<td>12.0</td>
<td>0.0011</td>
</tr>
<tr>
<td>CBV</td>
<td>0.093</td>
<td>69</td>
<td>9.0</td>
<td>0.041</td>
</tr>
<tr>
<td>MTT</td>
<td>15.7 s</td>
<td>64</td>
<td>2.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Table 3. Prediction of INFfinal vs OLI**

<table>
<thead>
<tr>
<th>Cutoff Value</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>F*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC</td>
<td>748×10⁻⁶ mm²/s</td>
<td>95</td>
<td>144</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ADCr</td>
<td>0.91</td>
<td>100</td>
<td>219</td>
<td>0.0001</td>
</tr>
<tr>
<td>CBF</td>
<td>37.2 cm³/min per 100 g</td>
<td>67</td>
<td>26</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CBV</td>
<td>0.088</td>
<td>65</td>
<td>40</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MTT</td>
<td>16.4 s</td>
<td>52</td>
<td>4.7</td>
<td>0.033</td>
</tr>
</tbody>
</table>

Sensitivity and specificity of initial absolute ADC, ADCr, and quantitative perfusion cutoff values to distinguish IGR from OLI area are shown.

Discriminant analysis was performed on 14 IGR and 38 OLI ROIs for ADCs (F₁,₈₃) and on 13 IGR and 37 OLI (degrees of freedom, F₁,₄₈) ROIs for quantitative perfusion data, because reliable quantitative perfusion measurements could not be obtained in 1 patient.

The best prediction was achieved with the ADC ratio, which correctly classified 84% of the regions, followed by CBF, absolute ADC, and CBV, all of which classified only 65% of the regions correctly. The INFfinal versus OLI discriminant analysis (Table 3) showed that the final size of the infarct was predicted more accurately by ADCr (95% of correct predictions) and ADC (88%) than by CBF (74%), CBV (72%), or MTT (58%). The ADC threshold value generated by the model was 748×10⁻⁶ mm²/s. This threshold was almost identical in the patients with infarct growth (group 1, 746×10⁻⁶ mm²/s) and the patients with stable or regressing lesions (groups 2 and 3, 749×10⁻⁶ mm²/s).

**Time Course of ADC Change**

The only significant effect of time was a negative correlation between absolute ADC value and time in the DWI ROI (r = −0.24, P = 0.005). Twenty-seven patients were imaged within 3 hours after stroke onset, and 21 patients were imaged 3 to 6 hours after stroke onset. There was no statistical difference in terms of age, European Stroke Scale score, initial infarct volume, or relative or absolute ADC values, although the latter tended to be lower in the 3- to 6-hour group (DWI 641±64×10⁻⁶ mm²/s, IGR 748±117×10⁻⁶, and OLI 822±45×10⁻⁶) than in the <3-hour group (DWI 677±67×10⁻⁶ mm²/s, IGR 809±32×10⁻⁶ mm²/s, and OLI 825±40×10⁻⁶ mm²/s).
mild degree of ADC decrease in the IGR region and the overlap between IGR and OLI individual values. It may also more fundamentally reflect the unpredictable outcome of the ischemic penumbra. To optimize the predictions, very recently, a pixel-by-pixel–based analysis conducted on 14 regions showed that the combination of DWI and PWI assesses the risk of infarction better than does DWI or PWI alone.\textsuperscript{30}

ADC Prediction of Final Size of the Infarct

We sought to determine whether ADC-based prediction of the final size of the infarct could be more accurate than the more subtle prediction of the IGR compartment. The INF versus OLI discriminant analysis generated an ADC threshold value of $748 \times 10^{-6}$ mm$^2$/s and an ADCr threshold value of 0.91, which correctly predicted 88% and 95% of the regions, respectively. This high accuracy is explained by the fact that the moderate ADC decrease in the IGR was combined with lower ADC values in the core of the infarct in patients with growing infaracts. Compared with prediction based on hemodynamic parameters, ADC-based prediction was more accurate and statistically more robust, with 5 to 10 times higher F values. We verified that the ADC thresholds were almost identical in the subgroups of patients with and without infarct growth. This suggests that an ROI-based prediction of the final size of the infarct could be performed prospectively without knowledge of the initial perfusion abnormalities and of the final tissue outcome. Finally, although the final size of the infarct corresponded to a heterogeneous region on the initial MRI inasmuch as it included the core of already infarcted tissue and the infarct growth area, it should be noted that a comparison of the initially visible qualitative DWI abnormality with the size of the computed quantitative ADC ROI may help to predict the extent of the true at-risk tissue. In other words, the ADC/DWI mismatch may be more efficient than the PWI/DWI mismatch at predicting the risk of infarct growth.

Limitations of the Study

The present study has some limitations. First, we defined the IGR and OLI regions partly retrospectively by using information not only from the initial MRI but also from the follow-up scan at days 2 to 4, which might not always represent the true final infarct.\textsuperscript{31} Prospective studies are needed to confirm our findings. Second, our patients did not receive thrombolytic treatments and are thus fairly representative of the natural course of ischemic stroke. Yet, part of the DWI hypersignal might be reversible in patients who underwent successful thrombolysis.\textsuperscript{21} Consequently, the IGR area might not embrace the entire potentially salvageable ischemic tissue if normal perfusion is rapidly restored. Conversely, the reversibility of the moderate ADC decrease found in the IGR area needs to be verified.\textsuperscript{20} Thus, the present ADC thresholds need to be compared with those in patients who received thrombolytics. Finally, it might be argued that the ADC threshold probably depends on the time elapsed after onset. Like Schlaug et al,\textsuperscript{17} we observed a moderate correlation between the time after onset and the ADC decrease in the core of the infarction. However, IGR and OLI ADC values were not significantly related to time. Because these results were based on different patients, the time dependence of ADC could have been masked by individual variations. Nevertheless, the lack of a clear-cut time dependence of the ADC values at the hyperacute stage\textsuperscript{32} suggests that the ADC thresholds could be equally valid during the first 6 hours after stroke.

Conclusions

We have shown that (1) ADC values are marginally but significantly decreased in the area of infarct growth; (2) ADC in the area that spontaneously escapes from infarction remains normal; and (3) ADC thresholds may be proposed to identify the at-risk tissue for individual patients. These results constitute a preliminary step toward a full characterization of the ischemic penumbra by using ADC alone. With further refinements, including data on diffusion anisotropy\textsuperscript{26,33} and improvement in ADC after processing,\textsuperscript{16,18,30} quantitative DWI might provide key data for rapidly predicting infarct growth in acute-stroke patients.

Acknowledgment

We thank Georges Oppenheim of the Laboratoire d’Analyse et de Mathématiques Appliquées at Marne-la-Vallée University for his assistance and helpful advice with the statistical analysis.

References

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Stroke. 2001;32:2486-2491
doi: 10.1161/hs1101.098331

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