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

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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 mm²/s, ADCr 0.94±0.08) compared with mirror values (P=0.01) and with OLI (ADC 823±41×10⁻⁶ mm²/s, ADCr 0.99±0.07; P=0.001). Of all quantitative DWI and PWI parameters, the ADCr best discriminated between IGR and OLI (F₁,₅₀=13.6, cutoff=0.97, 64% sensitivity, 92% specificity) and between the final volume of infarct and OLI (F₁,₈₃=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 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. 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. However, there is strong evidence that the PWI/DWI mismatch is an imperfect approximation of the true ischemic penumbra. First, qualitative indices are often used to determine the size of PWI abnormalities because PWI-based calculations of quantitative cerebral blood flow (CBF) values are time-consuming and rely on mathematical models that are still debated. In addition, the final size of the infarct is usually much smaller than the initial PWI/DWI mismatch area, and the exact prediction of infarct growth in a given patient remains extremely difficult.

Surprisingly little attention has been paid to early putative apparent diffusion coefficient (ADC) changes in the ischemic penumbra and in the at-risk tissue that will eventually evolve toward infarction. ADC changes in the core of the infarct have been extensively studied. In this area, a marked decrease in ADC results in a bright DWI hypersignal, which has become the hallmark of recent ischemic stroke. Yet, more subtle ADC changes remain invisible on DWI, and an early moderate decrease in ADC may occur in a true penumbra. In both animals and humans, a reversal of the DWI hypersignal or of ADC changes has been reported after extremely rapid reperfusion, confirming that ADC decrease may not always coincide with irreversible tissue damage.

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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 Echoprobe 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 System Inc). 25

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. 25 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 images, (2) the area with a prolonged apMTT on the initial apMTT map, and (3) the abnormal bright area on the follow-up FLAIR images. The ROI on the follow-up FLAIR images was redrawn in cases of large edematous infarcts so that the ROI matched the same anatomic area without edema. A PWI/DWI mismatch was considered present whenever the apMTT volume/DWI volume ratio exceeded 1.1 and the apMTT volume was larger than the INFfinal on follow-up FLAIR. The ROI on the initial ADC map was 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.

Four-hour postonset MRI and 3-day follow-up FLAIR in a patient with carotid T occlusion and acute right MCA infarction. Initially, the area of hemodynamic disturbance on the apMTT map (panel B, volume = 266 mL) was larger than the DWI hypersignal (panel A, volume = 76 mL) and larger than the INFfinal on follow-up FLAIR (panel C, volume = 98 mL, after correction for edema). The large PWI/DWI mismatch (volume = 42 mL) retrospectively divided into a growth ROI (IGR) was the difference between INFfinal and DWI, 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 INF$_\text{final}$ ROI and corresponded to the part of the mismatch area that remained viable (see Figure). The DWI, INF$_\text{imb}$, 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 Functool 1.9j software. ADC values were thresholded at 1200 mm$^2$/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, ADC ratios (ADCs) 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. Interobserver reliability for ADC values for each ROI was in all cases >93%. The volumes and the ADC, CBF, CBV, and MTT values reported in the results were averaged from the measurements obtained by the 2 observers.

**Statistical Analysis**

**Reproducibility**

Excellent interobserver correlation for quantitative volume and perfusion measurements using the same methodology has been reported elsewhere. Interobserver reliability for ADC values for each ROI was in all cases >93%. The volumes and the ADC, CBF, CBV, and MTT values reported in the results were averaged from the measurements obtained by the 2 observers.

**Descriptive Statistics**

We first compared ADC values obtained in the 4 ROIs (DWI, INF$_\text{imb}$, IGR, and OLI) to mirror ROIs by using paired Student t test because data were normally distributed. We then compared, within the infarcted side, DWI with INF$_\text{imb}$ ROIs >1 cm$^3$ and in IGR and OLI ROIs >1.5 cm$^3$ to minimize errors related to image coregistration and ROI drawing. Because of these size limitations, we obtained 47 DWI, 14 IGR, and 38 OLI measurements.

**Discriminant Analysis**

The aim was to determine whether early ADC and ADCr threshold values could predict infarct growth and final size and to compare ADC-based predictions with hemodynamic-based predictions on the basis of quantitative CBF, CBV, and MTT. Therefore, monovariate discriminant analyses testing IGR versus OLI and INF$_\text{imb}$ versus OLI were generated for each variable.

**Effect of Stroke Onset to MRI Delay**

The time dependence of ADC values in each ROI was tested by using a linear correlation test. In addition, the difference between ADC values in patients imaged within 3 hours and in those imaged between 3 and 6 hours after stroke onset was tested by using a nonparametric Wilcoxon test because data were not normally distributed.

**Results**

The volume of the lesion increased from 37±8 cm$^3$ (initial DWI ROI) to 44±6 cm$^3$ (INF$_\text{imb}$ 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 cm$^3$ (range 2.1 to 70 cm$^3$). In 29 patients (group 2), there was no infarct growth (0.3±1.4 cm$^3$). In the remaining 5 patients (group 3), there was a slight volume decrease (4.7±2.5 cm$^3$). An area of prolonged apMTT was observed in all but 2 patients, and as expected, its volume (114±86 cm$^3$) was much larger than that of initial DWI and final FLAIR abnormality. Accordingly, a PWI/DWI mismatch (mean volume 92±64 cm$^3$) 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.

**Infarct Growth Subgroups**

As shown in Table 1, absolute ADC and ADCr values gradually increased from the core to the periphery of the ischemic lesion. The absolute ADC values statistically differed from those on the contralateral side for both DWI ($P<0.001$) and IGR ($P=0.01$) but not for the OLI region ($P=0.07$). Paired comparisons within the infarcted side showed significant differences in ADC and ADCr values between INF and IGR ($P<0.001$, n=14) and between IGR and OLI ($P=0.001$, n=14). In the contralateral hemisphere, ADC values were not statistically significantly different (mirror INF 812±46×10$^{-6}$ mm$^3$/s, mirror IGR 829±43×10$^{-6}$ mm$^3$/s, and mirror OLI ROIs 829±40×10$^{-6}$ mm$^3$/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.
Sensitivity and specificity of initial absolute ADC, ADCr, and quantitative perfusion cutoff values to distinguish IGR from OLI area. Discriminant analysis was performed on 14 IGR and 38 OLI ROIs for ADCs (F_{1,9}) and on 13 IGR and 37 OLI (degrees of freedom, F_{1,48}) ROIs for quantitative perfusion data, because reliable quantitative perfusion measurements could not be obtained in 1 patient.

<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 803 × 10^{-6} mm²/s</td>
<td>74</td>
<td>5.6</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>ADCr 0.97</td>
<td>92</td>
<td>13.6</td>
<td>0.0006</td>
<td></td>
</tr>
<tr>
<td>CBF 38 cm³/min per 100 g</td>
<td>62</td>
<td>12.0</td>
<td>0.0011</td>
<td></td>
</tr>
<tr>
<td>CBV 0.093</td>
<td>62</td>
<td>9.0</td>
<td>0.041</td>
<td></td>
</tr>
<tr>
<td>MTT 15.7 s</td>
<td>64</td>
<td>2.6</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

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.

**ADC Prediction of Infarct Growth**

To address this issue, we divided a posteriori the PWI/DWI mismatch area into OLI (eventually noninfarcted) and IGR (eventually infarcted although normal on the initial DWI) regions. An OLI region was found in 79% of the patients, consistent with the fact that a PWI/DWI mismatch is a frequent finding in acute stroke and often remains uninfarcted. Conversely, an IGR region was found in only 29% of the patients, indicating that in a majority of patients, the initial DWI abnormality could approximate the final infarct size and that only ~1/3 of the patients are at risk of infarct growth. The main finding was that ADC values differed between OLI and IGR regions. They were normal in the OLI regions and mildly but significantly decreased in the IGR regions (6% mean decrease). The ADC values have only seldom been measured in the PWI/DWI mismatch area, but Schlaug et al. recently reported a mild reduction of ADCr in the IGR in 25 patients imaged up to 24 hours. Interestingly, the decrease in ADC (9%) was only slightly more marked than in the present study, suggesting that these subtle ADC changes surrounding the visible DWI abnormality may last longer than the classic 3- to 6-hour therapeutic window. The pathophysiological significance remains controversial. Schlaug et al suggested that these subtle ADC changes may reflect the presence of a subset of neurons with impaired ionic membrane gradients due to ATP depletion. However, experimental data suggest that a mild ADC decrease may reflect severe tissue acidosis or cortical spreading depression occurring in the penumbra rather than impairment of energy balance.

This is supported by the fact that ATP depletion with subsequent neuronal death occurred only in association with a more marked ADC reduction (≥10%). It has recently been shown that the distribution of ADC values was strongly correlated with the severity of perfusion deficit. In our sample of patients, discriminant analysis showed that ADC thresholds predicted IGR or OLI outcome as well or slightly better than MRI quantitative CBF and CBV thresholds. However, the accuracy of the prediction remained moderate, because only 65% of the regions were correctly classified by ADC or CBF absolute values. This reflects the...
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.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 of 748×10^{-6} mm²/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 infarcts. 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.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.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.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.,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 stage32 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 anisotropy26,33 and improvement in ADC after processing16,18,30 quantitative DWI might provide key data for rapidly predicting infarct growth in acute-stroke patients.

Acknowledgment
We thank Georges Oppenheim of the Laboratoire d’Analyses 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

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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