Apparent Diffusion Coefficient Thresholds Do Not Predict the Response to Acute Stroke Thrombolysis

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Background and Purpose—Apparent diffusion coefficient (ADC) thresholds for tissue infarction have been identified in acute stroke. IV tissue plasminogen activator (tPA) is associated with tissue salvage. We hypothesized that tPA would lower the ADC threshold for infarction.

Methods—ADC and mean transit time (MTT) maps were generated for 26 patients imaged within 6 hours of stroke onset (12 tPA and 14 conservatively managed controls). MTT maps and day-90 T2-weighted images were coregistered to ADC maps. Relative ADC (rADC) values were calculated for initial diffusion-weighted imaging (DWI) lesions, infarct growth regions (final infarct volume—the acute DWI lesion volume), and hypoperfused salvaged regions (HS; MTT map abnormality—the final infarct volume). When relevant, the DWI lesion was subdivided into DWI reversal and DWI infarct regions.

Results—Mean DWI lesion rADC was 0.79 in tPA and 0.74 in untreated patients (P=0.097). Mean rADC in HS and infarct growth regions were similar in tPA patients (0.950 and 0.946) and untreated patients (0.957, P=0.76; 0.970, P=0.08, respectively). The rADC in HS tissue was directly correlated with the time to treatment with tPA (r=0.685; P=0.029). DWI reversal was seen in 67% of tPA-treated patients and in 36% of those conservatively managed (Fisher exact test; P=0.238). In the 13 patients with DWI reversal, the mean rADC in these regions (0.81±0.07) was significantly higher than in the acute DWI region that infarcted (0.74±0.07; P=0.02), although no absolute thresholds could be identified.

Conclusions—The peri-DWI lesion region contains tissue with intermediate ADC values. The fate of this tissue is variable and cannot be predicted based on the ADC alone. DWI expansion occurs in bioenergetically normal tissue, and this is attenuated by tPA in a time-dependent fashion. (Stroke. 2005;36:2626-2631.)

Key Words: diffusion ▪ magnetic resonance imaging ▪ stroke ▪ thrombolysis

Perfusion-weighted imaging (PWI) and diffusion-weighted imaging (DWI) have been used with increasing frequency in acute ischemic stroke. PWI demonstrates areas of decreased blood flow, whereas DWI reveals regions of acute bioenergetic compromise. Stroke-tissue fate prediction studies have focused on mismatch between a larger PWI deficit and a smaller DWI lesion.1–4 Difficulties associated with obtaining and interpreting PWI have hindered its routine use in acute stroke. It would, therefore, be advantageous if tissue outcome in acute stroke could be predicted using DWI data alone.

DWI allows for ready identification of the ischemic lesion with high sensitivity and specificity.5 A quantitative measure of the degree of bioenergetic compromise in the ischemic lesion is provided by the apparent diffusion coefficient (ADC), a DWI-derived parameter. The probability of tissue infarction appears to be inversely proportional to the ADC. The lower the tissue ADC, the greater the degree of bioenergetic compromise and the more likely tissue is to infarct.6

Thrombolysis alters the fate of mismatch tissue by restoring blood flow and limiting DWI expansion. Thrombolysis has also been associated with recovery of abnormal-appearing tissue on the acute DWI lesion, with shrinkage of the initial volume.6–9 There is evidence that ADC thresholds for infarction and salvage exist.10 We studied the ADC thresholds of infarction in acute stroke patients treated with tissue plasminogen activator (tPA) or managed conservatively. We have shown previously, using PWI, that thrombolysis can rescue more severely hypoperfused tissue.11 We, therefore, hypothesized that the ADC threshold for infarction would be lower in patients treated with thrombolysis.

Methods

Patients
Twenty-six patients presenting with acute cortical stroke within 6 hours of symptom onset were included in this analysis. All of the

Received December 8, 2004; final revision received February 18, 2005; accepted April 11, 2005.
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Stroke is available at http://www.strokeaha.org

DOI: 10.1161/01.STR.0000189688.95557.2b

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patients were imaged acutely with cerebral computed tomography, followed by DWI and PWI scans. Twelve patients received thrombolysis with 0.9 mg/kg body weight tPA in accordance with the National Institute of Neurological Disorders and Stroke tPA Stroke Study protocol, with the exception that treatment time was extended to 6 hours. Patients were deemed ineligible for thrombolysis if stroke severity was mild (defined as National Institutes of Health Stroke Scale [NIHSS] score ≤4) or severe (defined as NIHSS score ≥22). The pretreatment computed tomography scan was used to exclude patients with hemorrhage or parenchymal ischemic changes exceeding one third of the middle cerebral artery territory. Treatment commenced immediately after MRI in all 12 of the tPA-treated patients. The imaging protocol and use of tPA were approved by the Human Research and Ethics Committee at our institution. Written informed consent was obtained from the patient or next of kin. The remaining 14 patients were historical controls, matched for age, time from stroke onset, and neurologic severity. They were recruited and imaged before the approval for the use of tPA in acute stroke at our hospital and were, therefore, managed conservatively.

MRI Protocol

MRI scans were obtained with a 1.5-T echo planar imaging-equipped whole-body scanner (Signa Horizon SR 120; General Electric). The baseline and subacute (days 3 to 5) studies included a T1-weighted sagittal localizer and DWI and PWI sequence. Day-90 studies included a T1-weighted sagittal localizer and T2-weighted, fast-spin double-echo sequence (repetition time/echo time per echo time, 3500/10 per 60 ms). Diffusion-weighted images were obtained with the use of a multislice, single-shot, spin-echo echo planar-imaging sequence. Sixteen 6-mm+1-mm gap slices were obtained. Matrix size was 256×256, field of view was 40×40 cm, and repetition time/echo time was 6000/107 ms. Diffusion gradient strength varied between 0 and 22 mT/m, resulting in 3 b-values of increasing magnitude from 0 to 1000 s/mm. Perfusion-weighted images were obtained with the use of a bolus of gadolinium diethylenetriaminopenta-acetic acid (0.2 mmol/kg) via a large-bore cannula in the antecubital fossa. The injection was performed at a speed of 5 mL/s with a power injector (Spectris, Medrad) and followed by a 15-mL bolus of saline. Ten to 13 slices were obtained, centered on the DWI lesion. Slice thickness was 6 mm+1-mm gap, matrix was 256×256, and field of view was 40×40 cm. Images were obtained at 40 time points/slice.

Data Analysis

Postprocessing of images was performed on a UNIX workstation using customized software developed in Interactive Data Language. Diffusion gradients were applied in 6 directions and averaged to form the isotropic diffusion map. ADC maps were calculated on a pixel-wise basis using the Stejskal-Tanner equation. Mean transit time (MTT) maps were generated by the nonparametric singular-value decomposition method described by Ostergaard et al.12,13 This method involves deconvolution of the tissue concentration-time curve on a pixel-by-pixel basis with an arterial input function. The shape of the arterial input function was determined from pixels located over the proximal middle cerebral artery of the unaffected hemisphere. The hypoperfused region was defined using a two-compartment model of blood flow and a time delay of 3 seconds beyond the contralateral hemisphere. The acute ADC, DWI, MTT, and day-90 T2-weighted imaging were coregistered using a 3D surface-matching algorithm (Analyze; Biomedical Imaging Research). Regions of interest (ROIs) were analyzed using standard planimetric techniques by an observer with knowledge of the side of the infarct but blinded to the clinical data. An upper threshold ADC value of 1200×10^-6 mm²/s was applied to eliminate cerebrospinal fluid. The ADC and volumes of individual ROIs were calculated. The corresponding contralateral homologous regions were defined by mirror reflection of ROI to the unaffected hemisphere. Relative ADC was calculated as a ratio of ADC values within each ROI to those in contralateral homologous regions. Acutely hyperintense lesions were manually outlined on the isotropic DWI images. The final infarct (INF) region was determined from the day-90 T2 image. The infarct growth region (IGR) was defined by subtracting the acute DWI lesion volume from the INF region volume. The hypo-perfused salvage region (HS) was defined by subtraction of the INF region volume from the acute MTT +4 seconds abnormality (Figure 1). In a subgroup of patients, the acute DWI lesion could be additionally subdivided into a DWI infarct region and a DWI reversal region. The DWI infarct region was defined as areas of the acute DWI lesion within the INF region borders. The DWI reversal region was defined as areas of the initial DWI lesion outside the INF region.

Statistical Analysis

Analysis was performed using a statistical software package (STATA statistical software). Regional ADC and relative ADC (rADC) values were compared with Student t tests. All of the correlation coefficients were tested with Pearson product moments.

Results

Baseline Patient Data

In tPA-treated patients, the mean age was 72 years (range, 58 to 86 years), mean time to MRI was 3.5 hours (range, 1.5 to 5.75 hours), and median NIHSS was 13.5 (range, 9 to 19). In conservatively managed patients, the mean age was 66.8 years (range, 45 to 83 years), mean time to MRI was 4.25 hours (range, 2 to 5.75 hours), and median NIHSS was 16.5 (range, 9 to 20). The tPA-treated and conservatively managed patients were matched with respect to age (P=0.20), time to MRI (P=0.10), and neurological impairment (P=0.29).

Regional ADC and rADC Analysis

In the 12 tPA-treated patients, the mean DWI lesion ADC was 739±135×10^-6 mm²/s. This corresponded to a rADC of 0.79 (Figure 1). Intermediate ADC values were found in the IGR (881±136×10^-6 mm²/s; rADC=0.95) and HS region (846±29×10^-6 mm²/s; rADC=0.95). Absolute and rADC values in the DWI lesion were significantly lower than the surrounding hypoperfused regions (P<0.001). In contrast, IGR and HS region ADC values were not significantly lower (P=0.80).

In the 14 conservatively managed patients, the mean DWI lesion ADC was 647±103×10^-6 mm²/s. The corresponding rADC was 0.74 (Figure 1). Intermediate ADC values were found in the IGR (844±94×10^-6 mm²/s; rADC=0.97) and HS region (838±112×10^-6 mm²/s; rADC=0.96). Absolute and rADC values in the DWI lesion were significantly lower than the surrounding hypoperfused regions (P<0.001). In contrast, IGR and HS region ADC values were not significantly lower (P=0.60).

The mean ADC in the DWI lesion did not differ between the tPA and conservatively treated patients (P=0.10). ADC values in the IGR (P=0.10) and HS (P=0.55) region were similar in the 2 patient groups (Table). A positive correlation between time to MRI and rADC in the HS region was found in tPA-treated patients (r=0.69, P=0.029; Figure 2). In contrast, rADC in the HS tissue did not appear to be related to time in the conservatively managed patients (r=-0.53; P=0.074).

Regional Volume Analysis

Mean volumes of the DWI lesion and IGR, HS and INF regions in tPA-treated patients were 37.6, 16.8, 44.7, and 42.1
The mean volumes of the DWI lesion and IGR, HS, and INF regions in conservatively managed patients were 67.3, 50.5, 33.5, and 110.5 mL, respectively (Table). DWI lesion expansion (outcome INF volume/DWI volume) was attenuated in tPA-treated patients (ratio 0.71) relative to those managed conservatively (ratio 1.80; P = 0.043). An inverse correlation between time and the volume of HS tissue was found in tPA-treated patients (r = -0.65, P = 0.045).

**DWI Reversal**

DWI reversal was seen in 67% of tPA-treated patients and in only 36% of those conservatively managed, but this difference was not significant (Fisher exact test, P = 0.238). In the 13 patients with DWI reversal, the mean rADC in these regions (0.81 ± 0.07) was significantly higher than in the acute DWI region that infarcted (0.74 ± 0.07; P = 0.02). Complete DWI lesion reversal was observed in 2 tPA-treated patients and none of those who were conservatively managed.

These 2 patients had only modestly decreased DWI rADC values of 0.90 at 3 hours and 0.99 at 5.75 hours. Another 6 tPA-treated patients demonstrated partial DWI reversal. The mean rADC in these regions was 0.81 ± 0.08, and this was not significantly different from the infarcted region (0.77 ± 0.05; P = 0.21). Five conservatively managed patients demonstrated partial DWI reversal. Mean rADC in these regions was 0.77 ± 0.05 and was not significantly different from that in the infarcted region (0.71 ± 0.04; P = 0.18). The mean rADC of the final infarct region in patients with no DWI reversal was 0.74 ± 0.07 (Figure 3).

**Discussion**

This study confirms that intermediate ADC values are present in hypoperfused tissue peripheral to the acute DWI lesion. The final fate of this tissue cannot, however, be predicted from the ADC in these regions alone. In addition, the ADC threshold for infarction in this oligemic tissue does not appear to be altered by thrombolysis, despite the fact that tPA increases salvage volume in these hypoperfused regions. Treatment with tPA also increases the probability of DWI reversal. Furthermore, the ability of tPA to promote reversal...
of the acute DWI lesion is inversely correlated with time to treatment.

**ADC in Oligemic Tissue**

Intermediate ADC values outside the acute DWI lesion have been reported previously. As in our study, these observed decreases in perilesional ADC values have been consistently moderate in magnitude (range, 1% to 17% decrease in ADC). This appears to reflect the fact that most of the hypoperfused tissue outside the acute DWI lesion is not bioenergetically compromised. With time, the DWI lesion expands into this previously unaffected tissue. Thus, ADC measurements alone do not differentiate the tissue destined to infarct from that amenable to salvage. This implies that acutely hypoperfused tissue with moderate bioenergetic compromise has a variable fate.

**DWI Reversal**

DWI reversal, or resolution of the acute DWI signal changes without subsequent infarction, is now well recognized in acute human stroke. Factors associated with DWI reversal include a shorter time interval to thrombolytic therapy, earlier reperfusion, and less severe decreases in ADC. Fiehler et al. showed that in less compromised tissue, 49% (by volume) of tissue with rADC of 70% to 80% demonstrated DWI reversal, but this was seen in only 6% of tissue with rADC <50%. DWI reversal was observed in 35.5% of patients imaged <3 hours after stroke onset and in only 8.1% of patients imaged 3 to 6 hours after stroke onset. Successful thrombolysis and reperfusion have also been reported to increase the likelihood of DWI reversal.

The probability of DWI reversal has been shown previously to be highly dependent on timely reperfusion. In the present study, DWI reversal was observed more frequently in tPA, relative to conservatively managed patients. In addition, partial DWI lesion salvage in the 4 conservatively managed patients was associated with spontaneous reperfusion. In patients with complete DWI reversal and, therefore, no infarct at 90 days, the decrease in ADC was extremely mild (rADC >0.90). Once again, however, there was significant overlap in tissue ADC values in the DWI lesion tissue that underwent reversal and that which ultimately infarcted. This precludes determination of an absolute threshold for DWI reversal.

**Time Dependency of ADC Thresholds**

The acute DWI lesion ADC values progressively decline during the acute phase of stroke. Patients imaged within 3 hours of symptom onset have higher ADC values than those imaged 3 to 6 hours after stroke. ADC values reach their nadir between 18.5 hours and 3 days. In our study, it is, therefore, not surprising that an absolute ADC threshold for infarction could not be identified, because it is likely to change with time. This is supported by our finding that the ADC of the salvaged tissue was correlated with the time to treatment with tPA. Thus, earlier treatment with tPA rescues tissue, which is more severely bioenergetically compromised. In those patients treated with tPA closer to 6 hours, DWI reversal only occurred in tissue with minimal ADC decreases. This is consistent with our previous finding that PWI thresholds for infarction are also highly time dependent. It has also been shown that the severity of the PWI deficit is positively correlated with the decrease in ADC. It appears, therefore, that increasing duration of hypoperfusion is associated with a progressive decline in tissue ADC and reduced probability of salvage. A larger study involving multiple imaging time points may assist in the development of a probability function based on ADC and duration of symptoms, although we would submit that identification of absolute ADC thresholds for infarction will not be practical clinically.

**Therapeutic Implications**

These findings do not support the hypothesis that a predictive model for tissue fate in acute ischemic stroke can be devel-

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**ROI ADC Values, rADC, and Volumes in tPA-Treated and Conservatively Managed Patients**

<table>
<thead>
<tr>
<th>ROI</th>
<th>Mean ADC ($\times 10^{-6}$ mm$^2$/s)</th>
<th>Mean rADC</th>
<th>Volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>tPA Treated</td>
<td>Conservatively Managed</td>
<td>$P$ Value*</td>
</tr>
<tr>
<td>DWI</td>
<td>739±135</td>
<td>647±103</td>
<td>0.07</td>
</tr>
<tr>
<td>IGR</td>
<td>881±136</td>
<td>844±94</td>
<td>0.46</td>
</tr>
<tr>
<td>HS</td>
<td>846±98</td>
<td>838±112</td>
<td>0.71</td>
</tr>
<tr>
<td>INF</td>
<td>766±111</td>
<td>722±102</td>
<td>0.34</td>
</tr>
</tbody>
</table>

* tPA-treated and conservatively managed patients.

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**Figure 2.** Scatter plot of time to MRI versus rADC in HS. In tPA-treated patients, a positive correlation between time and rADC is demonstrated ($r=0.685; P=0.029$).
oped using DWI data alone. Given the temporal evolution of the ischemic core and the ischemic penumbra, multimodality imaging with combined PWI and DWI is necessary to estimate tissue fate and the potential for intervention. However, it seems that ADC maps may be useful in predicting the likelihood of DWI lesion reversal. The utility of ADC values combined with semiquantitative PWI data in selecting patients for acute stroke therapy is currently being assessed. Thus, ADC maps may eventually be used in this manner to determine how much of the acute DWI lesion is potentially reversible and, therefore, should be regarded as penumbral.

**Conclusions**

The hypoperfused region outside the DWI lesion contains tissue with intermediate ADC values. The fate of tissue within and around the DWI lesion is variable and cannot be predicted based on the ADC alone. DWI expansion occurs into bioenergetically normal tissue, and this is attenuated by tPA in a time-dependent fashion. Thrombolysis increases the probability of DWI reversal.

**Acknowledgments**

P.-S.L. was supported by an Australian Postgraduate Award Scholarship (University of Melbourne) and the Royal Melbourne Hospital Neuroscience Foundation. We thank the radiographers at Royal Melbourne Hospital and Drs Amanda Lovell and Christopher Steward at the Brain Imaging Laboratory, Royal Melbourne Hospital, for their assistance with this study.

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