Background and Purpose—The apparent diffusion coefficient (ADC) derived from diffusion-weighted (DWI) MRI has been used to differentiate reversible from irreversible ischemic injury. However, the ADC can be falsely elevated by partial volume averaging of cerebrospinal fluid (CSF) with parenchyma, limiting the accuracy of this approach. This study tested the hypothesis that the accuracy of differentiating reversible from irreversible ischemic injury could be improved by CSF suppression at image acquisition.

Methods—Sixteen patients presenting within 6 hours from symptoms, and having partial reversal of the acute lesion on DWI were studied using conventional CSF-suppressed DWI. Lesions were segmented from coregistered acute DWI and follow-up fluid-attenuated inversion recovery (FLAIR) series. The segmented volumes were applied to conventional (ADCc) and CSF-suppressed ADC (ADCFlipd) maps to classify each voxel as progressed to infarct or reversed. Individual voxel ADC values were pooled across all patients. Sensitivity to predict reversal, specificity, and accuracy were calculated for both methods.

Results—A total of 25,313 voxels were classified as progressed and 31,952 voxels reversed. Across all lesion voxels, ADCflipd values more accurately depicted tissue fate compared with ADCc values (P<0.0001). The largest difference in the two methods was in voxels with <75% parenchyma, where the accuracy of ADCc was only 50% compared with 62% for ADCflipd.

Conclusion—CSF-suppressed ADC measurements gave a more accurate identification of reversible ischemic injury in this sample. We predict that multimodal MRI models of tissue viability in ischemic stroke will be more accurate if CSF-suppressed ADC measurements are used. (Stroke. 2004;35:1100-1106.)

Key Words: magnetic resonance imaging ■ cerebral ischemia ■ cerebrospinal fluid ■ stroke, acute

The accurate differentiation of potentially salvageable ischemic tissue from irreversibly damaged ischemic tissue is a goal of research aimed at optimizing the development and application of stroke therapies. Natural history studies of ischemic stroke have demonstrated that the volume of acute injury, as defined by diffusion weighted imaging (DWI) and the apparent diffusion coefficient (ADC), correlate with clinical severity and final infarct volume.1-4 While irreversible diffusion lesions tend to expand with time into regions of compromised cerebral perfusion,5-7 early restoration of blood flow to the ischemic area may prevent lesion progression, and the tissue injury potentially may normalize, without imaging evidence of subsequent tissue infarction.8-10

Several strategies have been used to predict tissue fate—recovery, progression to infarct, or hemorrhagic transformation—using ADC or perfusion parameters alone or in combination.11-21 These predictive models have used a range of approaches from identifying thresholds to predictions based on general linear statistical algorithms; from regional analysis to pooling voxel data across all patients. Per voxel analysis is based on the premise that the heterogeneity within the acute lesion may be informative and may be obscured by gross regional volumetric measures that average voxel values within a region.

Within an imaging voxel there can be a mix of normal and ischemic gray and white matter, vasculature and CSF; all with differing ADC.22 As the ADC of CSF is approximately 3 times that of normal tissue, voxels containing CSF can have falsely elevated ADC values due to partial volume averaging effects.23,24 Furthermore, the volume fraction of CSF varies throughout cortical and subcortical areas, eg, adjacent to sulci, ventricles, brain surface, perivascular spaces. Therefore, to best characterize the risk of the underlying tissue, these limitations of imaging need to be addressed.

Effective CSF-suppression has been demonstrated with fluid-attenuated inversion recovery (FLAIR) protocols, commonly used with T2-weighted imaging for chronic lesion identification.25,26 These techniques have been demonstrated...
to reduce the effect of CSF on ADC measurements when used in a DWI pulse sequence.\textsuperscript{27–29} We hypothesized that CSF-suppressed ADC would have greater predictive accuracy than conventional ADC.

Methods

Patient Selection

Patients who presented with acute stroke symptoms to our stroke center during June 2000 to July 2002 were consented to participate in a natural history protocol, approved by the appropriate Institutional Review Boards, and considered for this analysis. To distinguish the conventional DWI technique from CSF-suppressed DWI and FLAIR-T2 weighted imaging, we use the acronym of “FLIPD” for Fluid Inversion Prepared Diffusion.

To investigate the relative accuracy of FLIPD in distinguishing voxels that progress to infarct from those that may reverse to normal, we selected patients with evidence of partial lesion recovery. Patients met the following criteria: (1) discharge diagnosis of ischemic stroke; (2) acute imaging prior to the initiation of thrombolytic therapy, in patients who received alteplase; (3) DWI (b = 0, b = 1000), FLIPD (b = 0, b = 1000), and perfusion weighted imaging (PWI) exams of good quality within 6 hours of symptom onset; (4) a lesion >2 cm in greatest diameter within the cerebral hemispheres on acute conventional DWI examination; (5) FLAIR examination at least 20 days postictus; and (6) direct or indirect evidence of reperfusion determined by either 50% reduction of the volume of mean transit time (MTT) deficit within 24 hours, or reduction of at least 10% of the ischemic lesion volume on follow-up FLAIR imaging.

Imaging Protocol

Imaging was performed using a 1.5T clinical MRI system and the standard quadrature transmit-receive (TR) head coil. Two series of single shot echo planar (EPI) diffusion-weighted images were acquired: a conventional DWI protocol with repetition and echo times (TR/TE) of 6 s and 72 ms, respectively, and a FLIPD series (TR/TE = 9 s/72 ms, inversion time [TI] = 2.2 s), both with 128×128 matrix, field of view (FOV) = 240, and 20 contiguous but interleaved 7 mm slices. Images were acquired at b = 0 and b = 1000 with diffusion-weighting gradients along 3 orthogonal axes, for a total of 80 images per series, and a trace-weighted image was calculated by the MRI system software. Residual eddy currents typically resulted in distortion of less than 2 mm in any direction, with worst case of 3 mm in the most inferior slices. The distortion was equivalent in the conventional and CSF-suppressed techniques. Acute conventional FLAIR imaging was conducted with TR/TE = 9 s/98 ms, TI = 2.2 s, matrix of 256×256 and FOV = 240. FLAIR imaging at follow-up was of a higher resolution than the acute series, with slice thickness reduced from 7.0 to 2.0 mm. PWI was perfused using standard bolus tracking methods. Gadolinium-DTPA was administered at a dose of 0.1 mmol/kg via power injector (5 cc/s) during gradient EPI with TR/TE = 2 s/45 ms, matrix of 64×64, FOV = 240 and 20 axial slices acquired in 25 time series. Relative MTT maps were calculated using concentration-time curves obtained from the PWI series.

Lesion Segmentation

For each patient, the DWI b = 0 examination was first aligned to the anterior-posterior axis and the other image series was coregistered to it using a 7-parameter transformation model with trilinear interpolation and Normalized Mutual Information cost function (Medical Image Processing Analysis and Visualization, version 0.994u).\textsuperscript{30} Lesion segmentation was performed by an experienced reader, blinded to patient identifiers and clinical data. All acute lesions were segmented from the area of visible hyperintensity on conventional DWI exams. After all DWI exams had been evaluated, the area of hyperintensity on the follow-up FLAIR examination was segmented. In some cases, cortical retraction had developed within the boundaries of the chronic lesion. If the sulcus in that region was not evident on the acute FLAIR examination, the area of the sulcus was included within the follow-up FLAIR segmentation.

ADC maps were calculated from the acute DWI and FLIPD images in IDL (v5.6, Research Systems Incorporated) without thresholding. The segmented regions of interest (ROI) were then applied to both conventional ADC (ADC\textsubscript{C}) and FLIPD ADC (ADC\textsubscript{FLIPD}) maps to classify individual voxels as follows: (1) in both acute DWI and chronic FLAIR ROI (ischemic injury progressing to infarct); (2) in acute DWI, but not the chronic FLAIR ROI (ischemic injury reversing to normal); and (3) comparable contralateral hemisphere (normal control). The latter ROI was used for calculation of relative ADC\textsubscript{C} (rADC\textsubscript{C}) and was obtained by taking the acute DWI volume and mirroring it about the anterior-posterior axis to the contralateral hemisphere. The rADC\textsubscript{C} values of each voxel were calculated by dividing each voxel ADC\textsubscript{C} value by the mean ADC\textsubscript{C} of the patient’s contralateral control ROI. The relative parenchyma volume fraction for each of the voxels of interest was calculated from the FLIPD b = 0 and conventional DWI b = 0 according to previously published methods.\textsuperscript{24}

Data Analysis

For each patient, the mean ADC\textsubscript{C} and ADC\textsubscript{FLIPD} were calculated for the progressed and reversed regions. Voxel data then were combined across patients, and differences in the mean and variance among region categories were evaluated with Welch ANOVA, assuming unequal variances. Receiver Operating Characteristic (ROC) curves were created to assess the probability of correctly classifying a voxel given the ADC\textsubscript{C}, ADC\textsubscript{FLIPD} or rADC\textsubscript{C} value. From the areas under the curve (AUC), standard error, and correlation of diagnostic accuracy between methods, the difference between methods was evaluated using the statistical model of Hanley and McNeil\textsuperscript{31} for comparing 2 tests applied to the same population. Sensitivity (to predict reversal), specificity (to predict infarct), and accuracy were calculated for each subgroup along the continuum of possible discrimination thresholds for per patient data and pooled voxel data. True positives were data within the reversed category with ADC values that exceeded the discrimination threshold; false-negatives had subthreshold values. False-positives were progressed category data with suprathreshold ADC values; true negatives had subthreshold values.

Variation of ADC\textsubscript{C} and ADC\textsubscript{FLIPD} values with the relative parenchymal volume fraction of the voxel was tested with Pearson’s correlation. To further examine the effect of CSF on sensitivity, specificity, and accuracy, voxels within each region of interest were divided into subgroups based on the relative parenchymal volume fraction: <75%, 75% to 90%, and >90%. As CSF contamination is minimal for voxels with >90% parenchyma, the threshold values at maximum accuracy for this subgroup were determined for each method, and then applied across all voxels.

For each voxel, its ADC\textsubscript{C}, ADC\textsubscript{FLIPD}, and rADC\textsubscript{C} values were divided by the threshold proposed for that method. Voxelwise diffusion measurements greater than the threshold, therefore, had transformed values >1.0, whereas subthreshold values were less than 1. The differences of the paired transformed values were then ranked, and the Wilcoxon paired test was conducted. SPSS statistical software (version 11.0) was used for analyses.

Results

Patient and Lesion Characteristics

During the study period, 137 patients with a final diagnosis of ischemic stroke were imaged within 6 hours of symptom onset. Follow-up imaging >20 days was obtained for 45 of these patients, and 25 were considered for this study based on the criteria for reperfusion or lesion reversal. Two of these patients had a subsequent stroke during the follow-up examination period and 7 had acute lesions smaller than 2 cm in greatest diameter and were therefore excluded. Data on 16 patients were analyzed for this study, representing 57 265 acute lesion voxel data points (progressed n=25 313; reversed n=31 952) and an additional 57 265 contralateral
normal control voxels. Patient demographics are summarized in Table 1. All patients demonstrated at least 10% reversal of the acute DWI lesion (mean 72.7%, range 12% to 100%). The maximum accuracy distinguishing the two regions using ADC_C was 74% at a threshold value of 0.70×10⁻³ mm²/s. ADC_FLIPD was more accurate, to 81%, with a threshold value of 0.59×10⁻³ mm²/s.

### Pooled Voxel Characteristics

The pooled voxel data of the three categories (progressed, reversed, normal) were significantly distinct from each other within each modality (ADC_C: Welch ANOVA F=13912, P<0.001; ADC_FLIPD: Welch ANOVA F=33469, P<0.001). Progressed voxels had lower values (ADC_C mean 0.671±0.234, ADC_FLIPD mean 0.536±0.134), reversed were intermediate (ADC_C 0.753±0.253, ADC_FLIPD mean 0.622±0.142), and normal voxels had the highest values (ADC_C 1.063±0.455, ADC_FLIPD 0.807±0.168). Progressed voxels were more often distinguished from normal, based on ADC_FLIPD values, than based on ADC_C values (AUC_FLIPD 0.940, AUC_C 0.854; z=49.3, P<0.001). The same was true for distinguishing reversed voxels from normal (AUC_FLIPD 0.846, AUC_C 0.779; z=40.1, P<0.001). Of interest to this study was the direct comparison of voxels that progressed to infarct versus those that reversed. (Figure 1). For this analysis, the AUC for ADC_FLIPD (0.705; 95% CI 0.700 to 0.709) was larger than both ADC_C (0.623; 95% CI 0.618 to 0.627) and rADC_C (0.691; 95% CI 0.687 to 0.696). ADC_FLIPD was significantly more accurate than rADC_C (z=7.22, P<0.001) characterizing tissue reversal from progression. As the AUC for ADC_C was not large enough to be tested by the Hanley-McNeil method, significance could not be established for the comparison between ADC_FLIPD and ADC_C.

As demonstrated by the overlapping ROC curves for ADC_FLIPD and rADC_C, the diagnostic efficacy can vary along regions of the ROC plot. The threshold of optimal discrimination accuracy was calculated given the number of true and false-positives and -negatives at the ADC values along the ROC plot. ADC_C achieved a maximum diagnostic accuracy of 62% at a threshold of 0.57×10⁻³ mm²/s. The maximum accuracy of ADC_FLIPD and rADC_C were equal at 67%. The ADC_C threshold was 0.54×10⁻³ mm²/s. The rADC_C threshold was 0.53; when multiplied by the mean ADC_C of the normal ROI this equaled 0.56×10⁻³ mm²/s.

### Impact of CSF Contamination

Lesion ADC_C values correlated negatively with λ_p, the relative parenchymal volume fraction (r=-0.80, P<0.01). In this study, 21% of acute DWI lesion voxels had volume fractions <75%, and an additional 34% were in the 75% to 90% λ_p subgroup. These voxels were evenly distributed among the progress and reverse categories. The maximum accuracy of both methods was similar for voxels >90% parenchyma (69% ADC_C; 68% ADC_FLIPD), and converged at similar threshold values of 0.51 and 0.52×10⁻³ mm²/s respectively. Within this subgroup, the 2 methods differed most in their ability to characterize voxels that progressed to infarct, with ADC_FLIPD achieving a higher specificity of 60% compared with 49% for ADC_C (Table 2). These discrimination thresholds, 0.51×10⁻³ mm²/s and 0.52×10⁻³ mm²/s, were then applied to the <75% and 75% to 90% λ_p subgroups as well as the entire data set. The accuracy of ADC_C was observed to decrease to 50% for voxels with <75% paren-

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**TABLE 1. Patient Demographics**

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Symptom Onset to MRI (h)</th>
<th>Age/Sex</th>
<th>Admit NIH Stroke Scale</th>
<th>DWI Lesion (# voxels)</th>
<th>Treated with rtPA</th>
<th>Modified Rankin Score (90 days)</th>
<th>Stroke Mechanism (TOAST)</th>
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<td>72 F</td>
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<td>1331</td>
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<td>7</td>
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<td>616</td>
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<td>3579</td>
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</table>

(σd) (0.51) (17) (4343)
chyma. In this subgroup, all of the voxels were characterized as reversed due to suprathreshold ADC values, when, in fact, half of the voxels progressed to infarct. FLIPD methods were less affected by CSF contamination, attaining an accuracy of 67% to 68% for all of the categories except the subgroup, where accuracy decreased to 62%. In both conventional and FLIPD methods, all of the normal control voxels were above the threshold and therefore would be classified appropriately. Histograms categorized by volume fraction are shown in Figure 2. The threshold values determined by the pooled data were then applied to patient ADC and ADC FLIPD maps, to demonstrate spatial agreement with the actual final infarct volume. An example of a representative patient is shown in Figure 3.

Voxel ADC FLIPD was found to significantly differ from both ADC C (W = −168.85, P < 0.0001) and rADC C (W = −65.78, P < 0.0001). There were a greater number of voxels where the difference between the ADC C value and the threshold exceeded the difference between the ADC FLIPD value and corresponding threshold. Of the progressed voxels that were correctly classified according to the ADC FLIPD value, 6277 (25%) were misclassified by their ADC C values and 6056 (24%) misclassified by rADC C. At maximum accuracy, rADC C achieved higher sensitivity in characterizing voxels that reversed than did ADC FLIPD. However, the false-positive ratio (1-specificity) for rADC C was also higher: 56% as compared with 39% for ADC FLIPD.

Discussion

Predictive models to distinguish ischemic tissue at risk for infarction, but salvageable from tissue irreversibly injured have important clinical implications for the selection of acute stroke therapies. Identification of at-risk, but salvageable tissue as the target of thrombolytic therapy may help to safely expand the time window beyond 3 hours, and has been hypothesized as the optimal basis of patient selection for clinical trials of neuroprotective therapies. We have demonstrated that removal of the CSF contribution to ADC by acquiring the diffusion-weighted images based on FLAIR rather than T2-weighted b0 image, increased the accuracy of ADC in distinguishing viable from nonviable tissue. Although similar in accuracy to ADC thresholds identified in other studies, the ADC thresholds identified in this analysis are not proposed as a sufficient basis for clinical decision making. The goal of this study was not to determine a specific ADC threshold as an independent predictor of tissue outcome. Rather, it was to test the hypothesis that CSF partial volume had significant effects on ADC measurements and viability thresholds determined therefrom. A single parameter is unlikely to fully capture evolving ischemic pathology; hemodynamic, physiological, temporal, and therapeutic factors would all be expected to influence tissue viability. However, we have demonstrated that the accuracy of ADC contributions to tissue outcome prediction can be improved by suppression of CSF signal, suggesting that this approach may also improve the

| Table 2: Change in Sensitivity, Specificity, and Accuracy with CSF Contamination of ADC |
|----------------------|--------------|--------------|--------------|--------------|--------------|--------------|
|                     | Accuracy     | Sensitivity  | Specificity  |
|                     | ADC C        | ADC FLIPD    | ADC C        | ADC FLIPD    | ADC C        | ADC FLIPD    |
| >90% parenchyma     | 0.69         | 0.68         | 0.82         | 0.74         | 0.49         | 0.60         |
| 75-90% parenchyma   | 0.56         | 0.67         | 0.93         | 0.75         | 0.13         | 0.57         |
| 0-75% parenchyma    | 0.50         | 0.62         | 1.00         | 0.84         | 0.00         | 0.40         |
| All voxels          | 0.61         | 0.67         | 0.89         | 0.76         | 0.25         | 0.54         |

The discriminant threshold at maximum accuracy was determined for both conventional and FLIPD methods (ADC C, 0.51; ADC FLIPD, 0.52 × 10−3 mm²/s) based on the subgroup of voxels with >90% relative parenchymal volume fraction; therefore, minimizing the effects of CSF on the classification of voxel values. These thresholds were then applied to the subgroups of 0–75% and 75–90% parenchyma as well as the entire data set to assess the impact of CSF contamination on the sensitivity (identifying reversal), specificity (identifying progression to infarct), and accuracy of the methods.
accuracy of multiparametric predictive models for determining tissue viability and hemorrhagic risk.14–18,33

Combined algorithms18 have demonstrated that diffusion-based models differ from those of perfusion parameters, not in their overall accuracy, but in the trade-off between sensitivity and specificity. In the context of decision making for acute thrombolytic therapy, this balance of potential benefit and potential harm is of particular importance. Wu et al18 demonstrated that using rADC values to evaluate infarct progression resulted in a higher false-positive ratio for any given true-positive ratio. Our study was structured so that a higher specificity corresponded to correct classification of infarct progression. While ADCFLIPD and rADC C achieved similar maximum accuracy across the full range of lesion voxels, ADCFLIPD demonstrated greater specificity (61%) than rADC C (44%) and ADC C (40%). When the methods were compared at the optimal discriminant threshold determined by the subgroup of voxels with greater than 90% parenchyma (Table 2), the ability of ADC values to correctly predict infarct was reduced to only 25%, whereas the ADC FLIPD was only reduced to 54%.

Some models have used automated thresholding to reduce CSF contamination, for example, eliminating voxels above supranormal values such as 1.2×10⁻³ mm²/s. When applied to our data set, this filter did not improve the accuracy of either method. Notably, after the filter was applied to ADC C values, 21% of progressed and 14% of reversed voxels remaining still had <75% parenchymal volume fraction. This is a substantial volume of tissue still affected by CSF contamination and could have implications regarding treatment decisions. It should be noted that the CSF contaminated voxels were not restricted to the cortical surfaces (see Figure 3), and, thus, avoiding sampling from the cortical surface would not eliminate this problem.
The FLIPD examination was less than 2 minutes in duration, as part of a 15-minute multiparametric MRI protocol. While the signal to noise ratio of FLIPD is less than that of conventional DWI, all lesions were conspicuous on the FLIPD studies. Additionally, as ADC values can be decreased in perilesion areas, yet maintain normal DWI appearance, the accuracy of quantitative parameters is more important than visual contrast for the calculation of risk maps.

Several potential limitations of this study require discussion. Ours is a retrospective study and has the limitations inherent to that approach. Prospective confirmation of these results both as a single predictor and as part of a multivariate predictive model is important and is under way. We aimed to make the sample as homogeneous as possible with regard to time from onset, lesion size and location, and evidence of reversibility. The majority of the patients received intravenous recombinant tissue plasminogen activator (rtPA), but the improved accuracy with ADC_{FLIPD} was comparable between the patients who received rtPA and those who did not (results not shown).

The choice of the conventional rather than EPI FLAIR to delineate the chronic lesion was because of greater accuracy afforded by better spatial resolution and contrast to noise than on the b0 EPI, but this may have introduced image coregistration errors. Notwithstanding the noise that may be introduced by such misregistration, we found significant differences on our primary hypothesis, suggesting that such errors were not sufficient to obscure the differences between the acquisition methods.

The pooling of voxel data across patients has been the common approach to identifying thresholds in the prior literature because it can be prospectively applied in the acute setting, and, therefore, we adopted that method here. However, it assumes a complete independence of voxel measurements, which is unlikely to be the case. Voxel measurements within a patient, within a region, and across imaging modalities are likely to be correlated to some degree, and patients with larger lesions would have a relatively greater influence on the results. The effect could be minimizing the magnitude of group differences, while increasing the statistical power. We also compared ADC_{FLIPD} and ADC_{C} for each progressed and reversed regions on a per patient basis (see first paragraph of "Results"), confirmed a greater accuracy with either method, and a greater improvement in accuracies with ADC_{C_{FLIPD}}, but that difference was not statistically significant, due to the small sample size. Nonetheless, this regional analysis is consistent with the per voxel analysis.

Acute ischemic lesions in DWI contain heterogeneous ADC values with variable CSF contamination. Removal of CSF contamination provides a more accurate measurement of the underlying tissue ADC. As ADC has been proposed as one measurement to improve patient selection for thrombolytic and other acute stroke therapies, CSF-suppressed ADC measurements may be advantageous in testing the accuracy of predictive models of tissue viability and hemorrhagic risk. Accurate discrimination of salvageable from irreversibly damaged ischemic brain may also have implications for patient management and prognosis in the hyperacute period.

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References


More Accurate Identification of Reversible Ischemic Injury in Human Stroke by Cerebrospinal Fluid Suppressed Diffusion-Weighted Imaging

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