Background: Methods for determining cerebral blood flow (CBF) using bolus-tracking magnetic resonance imaging (MRI) have recently become available. Reduced apparent diffusion coefficient (ADC) values of brain tissue are associated with reductions in regional CBF in animal stroke models.

Objectives: To determine the clinical and radiological features of patients with severe reductions in CBF on MRI and to analyze the relationship between reduced CBF and ADCs in acute ischemic stroke.

Design: Case series.

Setting: Referral center.

Methods: We studied 17 patients with nonlacunar acute ischemic stroke in whom perfusion-weighted imaging (PWI) and diffusion-weighted imaging (DWI) were performed within 7 hours of symptom onset. A PWI-DWI mismatch of more than 20% was required. We compared patients with ischemic lesions that had CBF of less than 50% relative to the contralateral hemisphere with patients with lesions that had relative CBF greater than 50%. Characteristics analyzed included age, time to MRI, baseline National Institutes of Health Stroke Scale score, mean ADC, DWI and PWI lesion volumes, and 1-month Barthel Index score.

Results: Patients with low CBF (n=5) had lower ADC values (median, 430 × 10⁻⁶ mm²/s vs 506 × 10⁻⁶ mm²/s; \( P = .04 \)), larger DWI volumes (median, 41.8 cm³ vs 14.5 cm³; \( P = .001 \)) and larger PWI lesions as defined by the mean transit time volume (median, 194.6 cm³ vs 69.3 cm³; \( P = .01 \)), and more severe baseline National Institutes of Health Stroke Scale scores (median, 15 vs 9; \( P = .02 \)).

Conclusion: Ischemic lesions with severe CBF reductions, measured using bolus-tracking MRI, are associated with lower mean ADCs, larger DWI and PWI volumes, and higher National Institutes of Health Stroke Scale scores.

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PATIENTS AND METHODS

PATIENTS

We retrospectively identified patients with acute ischemic stroke entered into the Stanford Stroke Center database in whom DWI and PWI were obtained within 7 hours of symptom onset. Patients had to have an acute PWI lesion volume (defined as the MTT lesion, see the “Postprocessing of Perfusion Images” section) that was 20% larger than the volume of the acute DWI lesion. We excluded patients without a PWI-DWI mismatch because it is thought that these patients have spontaneous or treatment-induced reperfusion, and their PWI variables do not reflect values before reperfusion. Treatment with recombinant tissue plasminogen activator and enrollment in trials of neuroprotective agents vs placebo were allowed. The following clinical characteristics were recorded: age, NIHSS score, time from symptom onset to MRI, and functional outcome measured using the Barthel Index 1 month after stroke onset. Patients who died during the first month of follow-up were assigned a Barthel Index score of zero. The study was approved by the Stanford University institutional review board.

MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging was performed using echoplanar imaging on a 1.5-T magnet (Signa; General Electric, Milwaukee, Wis). Multislice whole-brain DWI was performed using the following variables: 16 slices; repetition time, 8100 milliseconds; echo time, 110 milliseconds; slice thickness, 5 mm; gap, 2.5 mm; matrix, 128 × 128; and field of view, 24 cm. B values were 0 and 829 s/mm². Diffusion-weighted images were acquired in the x, y, and z directions. The x-, y-, and z-direction DWI scans were averaged to minimize hyperintensities due to anisotropic water diffusion. Echoplanar diffusion images were processed to generate average (trace) ADC maps using a computer program (MRVision; MR Vision Co, Winchester, Mass).

Perfusion-weighted imaging was performed using dynamic susceptibility contrast-enhanced MRI. Gradient-echo, single-shot echoplanar imaging was used during injection of 20 mL of gadolinium (0.2 mmol/kg). Perfusion-weighted imaging acquisition values were repetition time, 2000 milliseconds; and echo time, 60 milliseconds, with 40 time points obtained over 12 slices. Other variables were the same as for DWI. The 12 PWI slices were obtained at the same level as the 12 central slices on the DWI scans. The raw images were transferred to a computer workstation (Sun Ultrasparc; Sun Microsystems, Palo Alto, Calif) for further analysis.

POSTPROCESSING OF PERFUSION IMAGES

Calculation of relative MTT, relative CBF, and relative CBV maps was performed using the model-independent NP-SVD method described by Ostergaard et al. The tissue concentration curve was deconvolved with the arterial input function using SVD. We determined the arterial input function by manually choosing 5 to 9 pixels over the MCA of the unaffected hemisphere. These pixels had to show an

lowest ADC. Regions with less severe reductions in CBF show either normal ADC or only mild reductions. For example, Dijkhuizen et al reported that after a 1-hour middle cerebral artery (MCA) occlusion in rats, the ADC was severely reduced in areas where CBF was reduced to less than 20% of normal. A modest reduction or no reduction at all was observed in areas where CBF was reduced to 40% to 60% of normal. We attempted to validate the CBF measurement indirectly by comparing CBF with other accepted and easily measured markers of stroke severity.

Clinical studies have shown a high correlation between the volumes of DWI and PWI lesions and clinical impairment scales such as the National Institutes of Health Stroke Scale (NIHSS). These volumes also seem to partially predict functional outcome. Because the primary consequence of a vessel obstruction due to clot is a reduction in CBF, we studied the impact of a severe reduction in CBF, measured using dynamic susceptibility contrast imaging, on the size of DWI and PWI lesions and on clinical stroke severity and functional outcome. We tested the hypothesis that in acute human ischemic stroke, low CBF values were associated with lower ADC values, larger DWI and PWI lesion volumes, and higher baseline NIHSS scores.

RESULTS

Twenty-nine patients were identified who underwent DWI and PWI within 7 hours of symptom onset between August 1, 1996, and August 1, 2000. Eight patients did not have a PWI-DWI mismatch. In 4 patients, poor image quality due to motion artifact or inadequate bolus delivery prevented analysis of the perfusion images. This left 17 patients for analysis. Median age was 73 years (25th-75th percentile, 65-79 years). Nine patients were women (53%). The clinical and radiological characteristics of the patients are given in the Table. The median baseline NIHSS score was 10 (25th-75th percentile, 8-15). Three
earlier increase in intensity and a 3- to 9-fold larger peak on the tissue concentration time curve compared with the curves obtained from normal brain parenchyma. To determine relative CBV, the tissue concentration over time curve was numerically integrated between bolus arrival and the moment at which the tissue concentration curve in affected tissue had again completely or almost completely returned to baseline. Mean transit time was calculated from these measurements as CBV/CBF according to the central volume principle.

VOLUMETRICS AND INTENSITY MEASUREMENTS

Lesion volume measurements were performed by manually outlining the lesions on the DWIs and the MTT maps. The regions of interest (ROIs) identified on the MTT maps were transferred to the CBF and CBV maps (Figure 1). Mean intensities were measured in the MTT, CBV, and CBF ROIs and compared with reference values. The reference MTT value was obtained by manually outlining a large part of the contralateral MCA on 3 central slices of the MCA and calculating the mean intensity within these regions. The same ROIs were chosen to determine the reference CBV and CBF values. To obtain lesion volumes, the abnormal areas on the images were summed and multiplied with the slice thickness plus interslice gap.

To test interobserver variability, 2 observers (V.N.T., A.A.) independently drew ROIs in 17 randomly sampled MTT images and measured their mean intensity. The interobserver reliability of the measurement of the intensity of the MTT and the volume of the MTT lesions was excellent ($r > 0.95$). The DWI lesion volumes were measured by 2 independent observers (V.N.T., A.A.) and were averaged. High interobserver reliability was found ($r > 0.95$).

ADC MEASUREMENTS

The abnormality outlined on the DWIs was subsequently transferred to the corresponding ADC map (Figure 2). The ADC$_{550}$ was determined by identifying all the pixels below the threshold of $550 \times 10^{-6}$ mm$^2$/s and calculating the mean ADC value within these pixels. The threshold of $550 \times 10^{-6}$ mm$^2$/s corresponds approximately to a 40% reduction in the normal ADC ($880 \times 10^{-6}$ mm$^2$/s).$^{18}$ The ADC$_{550}$ was ranked in ascending order. Patients without DWI lesions or in whom no pixels were found below the threshold of $550 \times 10^{-6}$ were assigned the highest rank. Non-parametric statistics, based on rank order, were used for all statistical calculations.

STATISTICS

We compared age, time to MRI, NIHSS scores, initial DWI volumes, initial PWI volumes, and the mean ADC as well as the absolute mismatch volume, CBF, and CBV between patients with severe reductions in CBF (CBF $< 50\%$) and patients with moderate to mild CBF reductions (CBF $> 50\%$). The Mann-Whitney test was used for these calculations. We correlated the total distribution of CBF with the same clinical and radiological characteristics using the Spearman rank correlation coefficient. Statistical analysis was performed using a computer program (SPSS 10.0; SPSS Inc, Chicago, Ill).
49%), and group 2 (n=12) comprised patients with CBF values greater than 50% (range, 52%-116%). Comparison of the 2 groups is detailed in Figure 3 and Figure 4.

Patients in group 1 had lower ADC values than patients in group 2. Group 1 patients had larger DWI volumes (median, 41.8 cm³; 25th-75th percentile, 35.1-131.1 cm³ vs median, 14.5 cm³; 25th-75th percentile, 1.7-26.9 cm³; \( P = .04 \) vs group 2) and PWI volumes (median, 194.6 cm³; 25th-75th percentile, 121.5-250.0 cm³ vs median, 69.3 cm³; 25th-75th percentile, 41.6-118.1 cm³; \( P = .01 \)). Group 1 patients had more severe clinical strokes (NIHSS score: median, 15; range, 9-23 vs median, 9; range, 4-22; \( P = .02 \)). Their MTT and CBV values were not significantly different. The functional outcome between the 2 groups was not significantly different, although there was a trend of worse functional outcomes in group 1 (Barthel Index score: median, 20; 25th-75th percentile, 15-95 vs median, 85; 25th-75th percentile, 45-100; \( P = .16 \)).

We did not find a correlation between the total distribution of CBF and the ADC values (\( P = .24 \)), NIHSS score (\( P = .42 \)), or Barthel Index score (\( P = .18 \)). The CBF was significantly correlated only with DWI lesion volume (Spearman \( \rho = -0.555; P = .02 \)). A nonsignificant correlation was found between CBF and PWI lesion volume (Spearman \( \rho = -0.446; P = .08 \)).

### Clinical and Radiological Features of Patients in Groups 1 and 2

<table>
<thead>
<tr>
<th>Time From Symptom Onset to MRI, h</th>
<th>Relative CBF, %</th>
<th>Relative MTT, %</th>
<th>Relative CBV, %</th>
<th>Lesion Volume, cm³</th>
<th>ADC&lt;sub&gt;550&lt;/sub&gt;, ×10⁻⁶ mm²/s</th>
<th>Baseline NIHSS Score</th>
<th>Barthel Index Score†</th>
<th>DWI</th>
<th>PWI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>27.2</td>
<td>1298.1</td>
<td>361.8</td>
<td>41.8</td>
<td>194.6</td>
<td>442</td>
<td>15</td>
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<td></td>
</tr>
<tr>
<td>4.5</td>
<td>28.3</td>
<td>1329.3</td>
<td>140.2</td>
<td>153.2</td>
<td>243.1</td>
<td>430</td>
<td>23</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>5.0</td>
<td>40.0</td>
<td>1147.9</td>
<td>206.0</td>
<td>35.9</td>
<td>93.0</td>
<td>357</td>
<td>9</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>5.0</td>
<td>41.0</td>
<td>370.0</td>
<td>140.0</td>
<td>109.2</td>
<td>257.0</td>
<td>342</td>
<td>22</td>
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<tr>
<td>7.0</td>
<td>49.0</td>
<td>271.5</td>
<td>130.6</td>
<td>35.2</td>
<td>150.0</td>
<td>432</td>
<td>15</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

**Group 1 (n = 5):**

- Median (25th-75th percentile): 5.0 (4.5-6.0), 58 (45-73), 329 (248-684), 162 (129-209), 24.7 (6.5-35.5), 93.0 (54.2-177.7), 436 (408-505), 10 (8-15), 70 (15-95)

**Group 2 (n = 12):**

- Median (25th-75th percentile): 6.0 (5.5-6.5), 52.1 (47.5-57.0), 461.1 (384-538), 216.8 (150-300), 20.0 (15-25), 74.4 (50-100), 441 (320-560), 6 (4-8), 85 (70-90)

- Median (25th-75th percentile): 6.8 (6.0-7.5), 52.6 (47.5-57.0), 305.5 (240-450), 161.5 (100-240), 8.1 (5-10), 94.7 (60-120), 504 (360-680), 13 (8-18), 85 (60-100)

- Median (25th-75th percentile): 5.5 (4.5-6.5), 53.1 (47.5-57.0), 264.8 (200-350), 115.2 (70-150), 23.1 (15-30), 64.1 (40-90), 452 (300-600), 6 (4-8), 50 (30-70)

- Median (25th-75th percentile): 2.6 (2.0-3.0), 58.3 (45-73), 272.5 (200-400), 190.4 (100-250), 0 (0-5), 199.2 (120-250), \( \ldots \) (100-200), 4 (2-6), 100 (50-150)

- Median (25th-75th percentile): 6.6 (5.5-7.5), 60.0 (45-73), 579.0 (400-750), 230.0 (150-350), 28.3 (15-40), 39.4 (20-60), 417 (300-600), 9 (6-12), 65 (40-80)

- Median (25th-75th percentile): 4.0 (3.5-4.5), 60.5 (45-73), 219.5 (150-300), 105.3 (70-200), 5.0 (3-10), 10.7 (5-15), \( \ldots \) (4-10), 4 (2-6), 100 (50-150)

- Median (25th-75th percentile): 5.9 (5.0-6.5), 64.3 (47.5-70.0), 989.7 (750-1250), 26.2 (15-40), 0 (0-5), 20.3 (10-30), \( \ldots \) (9-15), 9 (6-12), 100 (50-150)

- Median (25th-75th percentile): 3.5 (2.5-4.0), 70.0 (55-80), 233.0 (150-350), 136.0 (100-200), 27.7 (20-40), 60.2 (30-90), 513 (300-700), 9 (6-12), 13 (8-18)

- Median (25th-75th percentile): 5.8 (5.0-6.5), 76.3 (55-80), 451.8 (350-600), 200.8 (100-300), 9.1 (5-15), 80.2 (40-100), 513 (300-700), 8 (6-10), 0 (0-2)

- Median (25th-75th percentile): 4.8 (4.0-5.5), 86.0 (60-120), 771.9 (500-1000), 211.0 (100-300), 0.7 (0-5), 48.3 (20-80), 509 (300-700), 22 (10-40), 85 (40-100)

- Median (25th-75th percentile): 6.0 (5.0-7.0), 96.0 (70-120), 188.0 (100-250), 127.0 (100-200), 30.8 (20-50), 125.9 (70-150), 422 (200-600), 10 (8-15), 100 (60-120)

- Median (25th-75th percentile): 4.6 (3.5-5.0), 116.0 (80-150), 189.0 (100-250), 163.0 (100-200), 24.7 (15-30), 160.7 (80-200), 380 (200-600), 14 (10-20), 45 (20-70)

*Group 1 refers to patients with a cerebral blood flow (CBF) <50%, and group 2 refers to patients with CBF >50%. MRI indicates magnetic resonance imaging; MTT, mean transit time; CBV, cerebral blood volume; DWI, diffusion-weighted imaging; PWI, perfusion-weighted imaging; ADC<sub>550</sub>, mean of all apparent diffusion coefficient values in pixels below the threshold of 550 × 10⁻⁶ mm²/s; NIHSS, National Institutes of Health Stroke Scale; and ellipses, no value could be obtained.

†Measured 1 month after stroke onset.

**Figure 2.** Diffusion-weighted imaging and apparent diffusion coefficient (ADC) maps from the patient shown in Figure 1. A, Diffusion-weighted imaging map showing a right middle cerebral artery distribution lesion. B, An ADC map with the region of interest transferred from part A. C, An ADC map. Highlighted pixels within the region of interest represent pixels with an ADC value of less than 550 × 10⁻⁶ mm²/s (mean, 342 × 10⁻⁶ mm²/s).
Our findings suggest that low CBF values, measured with bolus-tracking MRI, are associated with lower ADC values, larger DWI and PWI lesion volumes, and more severe NIHSS scores. The association between CBF and the ADC or NIHSS scores was not evident when comparing CBF with ADCs and NIHSS scores across the whole range of CBF values.

We did not measure CBF directly in our study. The ROIs used to measure CBF were derived from the areas of hyperintensity measured on the MTT maps. Choosing the MTT as the ROI probably causes overestimation of CBF. The MTT lesion includes areas that vasodilate in response to decreasing cerebral perfusion pressure and, therefore, have increased MTT but have not reached the threshold for a reduction in CBF. The finding of CBF increases, rather than decreases, in our ROI suggests that vasodilatation often occurred within the studied ROI. The overestimation of CBF due to our measurement method might explain the absence of an overall relationship between CBF and the ADC. Another explanation might be that ADC reductions are only associated with CBF reductions below a certain threshold. This explanation is backed by experimental data demonstrating that DWI hyperintensities, or ADC reductions, occur only at specific levels of CBF reduction that persist over certain amounts of time. The information gained from PWI and DWI represents an evaluation of the cerebral ischemic process at a single time point, and this might also explain the lack of correlation between these variables.19,20

We chose MTT maps to measure the ROI because the borders of MTT lesions are easier to delineate on PWI than CBF or CBV maps. Differences in CBF and CBV between gray and white matter, combined with the presence of only mild changes in CBF and CBV, compared with MTT, make visual delineation of the border of the lesions on CBF and CBV more difficult, especially in white matter and at the gray/white matter junction.21

The results of our study confirm the relationship between reductions in CBF and low ADC values found in animal models of ischemic stroke.19,22 Sorensen et al23 assessed the relationship between hemodynamic factors and the ADC in 23 patients with acute ischemic stroke studied within 12 hours of symptom onset. This study did not find a correlation between the overall ADC and CBF. The authors did not compare the association between the lowest CBF values and the ADC. The association of low CBF with other indicators of stroke severity, such as a low ADC, large DWI lesion volumes, and higher NIHSS scores, provides partial concurrent validation of the MRI method for measuring relative CBF. Our findings suggest that in future studies, low ADC values could be used as surrogates for low CBF values. Other studies have compared this NP-SVD MRI method of measuring hemodynamics with noninvasive CBF measurements in humans. Lie et al24 compared the NP-SVD MRI method with a spin-labeling MRI technique in healthy volunteers and found good agreement between both techniques. Liu et al25 found a curvilinear relationship between relative CBF values obtained using single-photon emission computed tomography and the NP-SVD MRI method in 11 patients with acute ischemic stroke. The same group26 also reported a high correlation between hypoperfusion volumes obtained using single-photon emission computed tomography and the NP-SVD MRI method in 23 patients. A nonsignificant trend of worse functional outcome in patients with low CBF values was found. The absence of a significant association is probably related to the small sample size, although this hypothesis should be confirmed in further studies. Van Everdingen et al27 reported significant correlations between ADC values and indicators of functional outcome in 38 patients with acute ischemic stroke.

The limitations of our study are related to the small sample size and the performance of multiple-hypothesis
testing. We arbitrarily chose a reduction in CBF of greater than 50% to distinguish between severe CBF reduction and less severe CBF reduction. We were not able to analyze the spatial correspondence between a low ADC and reduced CBF values in individual voxels because the baseline DWIs and PWIs were not coregistered. The bolus-tracking MRI technique has some inherent limitations. Absence of contrast delivery in nonperfused regions makes accurate measurement of CBF within these areas impossible. Delays in contrast arrival through collateral vessels or dispersion of contrast through a stenosis may mimic decreases in CBF, although beneficial perfusion is present. Accurate determination of the arterial input function required to perform deconvolution with the tissue concentration time curve is subject to errors caused by partial volume artifacts.

In conclusion, we found an association between reduced CBF measured using MRI and clinical and radiological markers of stroke severity. This association was present only with severe reductions in CBF.

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