Clinical-Diffusion Mismatch Predicts the Putative Penumbra With High Specificity

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Background and Purpose—Perfusion-diffusion (PWI-DWI) mismatch may represent the ischemic penumbra. The complexities associated with perfusion-weighted imaging (PWI) have restricted its use. Mismatch between stroke severity, assessed with the National Institutes of Health Stroke Scale (NIHSS), and the volume of the diffusion-weighted imaging (DWI) lesion (clinical-diffusion mismatch; CDM) has been suggested as a surrogate for PWI-DWI mismatch. We compared CDM with PWI and DWI in acute stroke.

Methods—Seventy-nine hemispheric stroke patients were imaged within 24 hours of symptom onset and subacutely (3 to 5 days). CDM was defined as NIHSS ≥8 and DWI ≤25 mL. DWI lesion and PWI (Tmax ≥4s) volumes were measured by planimetric techniques. Acute PWI-DWI mismatch was examined as a continuous variable (mismatch volume = PWI_vol − DWI_vol) and a categorical variable (mismatch = PWI_vol − DWI_vol / DWI_vol × 100 ≥20%). Early infarct expansion was calculated as DWI_subacute_vol / DWI_acute_vol.

Results—In the 54 sub–6-hour patients, CDM detected PWI-DWI mismatch with a specificity of 93% (95% confidence interval [CI], 62% to 99%), a positive predictive value of 95% (95% CI, 77% to 100%), but a sensitivity of only 53% (95% CI, 34% to 68%). Alternate DWI and NIHSS cutpoints did not improve test performance characteristics. In addition, subacute DWI expansion was significantly greater in patients with CDM (P = 0.01) compared with those without.

Conclusions—CDM (NIHSS ≥8, DWI ≤25 mL) predicts the presence of PWI-DWI mismatch with high specificity and low sensitivity. CDM also predicts DWI expansion. CDM may be a useful selection tool in acute stroke therapies, including thrombolysis. (Stroke. 2005;36:1700-1704.)

Key Words: stroke, acute ■ magnetic resonance imaging, diffusion weighted ■ diagnostic imaging
■ magnetic resonance imaging, perfusion weighted

Thrombolytic therapy in acute stroke patients is presently limited to the 3-hour time window developed in clinical trials.1 If the time window is to be extended, more refined selection strategies are required. The ischemic penumbra is a variable region of critically hypoperfused but potentially salvageable tissue.2 The volume of penumbral tissue typically decreases with time as the infarct expands, but the duration of the potential therapeutic window is variable.3 Rapid, accurate detection of the presence and extent of penumbral tissue may permit thrombolysis to be delivered on the basis of each patient’s unique stroke pathophysiology.

Diffusion-weighted imaging (DWI) identifies bioenergetically compromised tissue, and perfusion-weighted imaging (PWI) allows visualization of hypoperfused tissue.4,5 Mismatch between a larger PWI lesion and a smaller DWI lesion has been proposed to approximate the ischemic penumbra.6 It is now appreciated that the diffusion lesion may include potentially salvageable tissue, and the perfusion lesion may include regions of benign oligemia, but MRI is noninvasive and widely available.7,8 A clinical trial to test the hypothesis that the presence and extent of PWI-DWI mismatch will predict the response to thrombolysis is under way.9 DWI is commonly used in acute stroke assessment, but the technical complexities associated with PWI and uncertainty regarding interpretation have limited its routine clinical use. A reliable method of detecting the presence of penumbral tissue without PWI would therefore be valuable. On the basis of the assumption that stroke severity is more closely correlated with acute PWI volume than DWI volume, Davalos and coworkers10 demonstrated that mismatch between stroke severity (assessed with the National Institutes of Health Stroke Scale [NIHSS]) and the volume of the DWI lesion predicted infarct expansion and response to thrombolysis. An NIHSS ≥8 combined with a DWI volume ≤25 mL was defined as a clinical-diffusion mismatch (CDM), but no direct comparison with perfusion-diffusion mismatch was made.
We hypothesized that CDM would predict PWI-DWI mismatch in addition to subacute DWI lesion expansion.

Subjects and Methods

Patient Selection
Patients were retrospectively accrued from the stroke service of a major teaching hospital between 1999 and 2003. Patients presenting with sudden onset of a neurologic deficit consistent with a cortical ischemic stroke who underwent emergent DWI and PWI imaging within 24 hours of stroke onset were eligible. Patients with cerebral hemorrhage or clinical syndromes consistent with lacunar and brainstem stroke were excluded. The MRI and clinical studies were approved by the Human Research and Ethics Committee at our institution, and written, informed consent was obtained from the patient or next of kin in all cases.

Stroke onset was defined as the last time the patient was known to be without a neurologic deficit. Clinical assessment including NIHSS was performed by a stroke neurologist or trainee accredited in NIHSS administration immediately before MRI. Subacute MRI was performed in surviving patients 3 to 5 days after symptom onset. Patients treated with recombinant tissue-type plasminogen activator was performed in surviving patients 3 to 5 days after symptom onset. Patients treated with recombinant tissue-type plasminogen activator or enrolled in a thrombolyis trial, those with evidence of hemorhagic transformation causing mass effect, and those without a subacute scan were excluded from outcome analyses (n=30).

Definitions
CDM was initially defined as an NIHSS ≥8 and DWI ≤25 mL.10 Acute PWI-DWI mismatch was examined as a continuous variable, defined as mismatch volume=PWIVol−DWIVol. PWI-DWI mismatch was also assessed as a categorical variable, defined as mismatch=PWIVol−DWIVol×100>20%.11,12 Subacute DWI expansion was calculated as DWIsubacute vol/DWIacute vol.

MRI Protocol
MRI scans were obtained with a 1.5-T echoplanar imaging-equipped whole-body scanner (Signa Horizon SR 120; General Electric). MRI studies were completed at baseline and 3 to 5 days after symptom onset. Sequences included a T1-weighted sagittal localizer, DWI, PWI, and phase-contrast MRA.

PW images were obtained with a bolus of gadolinium Gd-DTPA (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, with slice thickness 6 mm a with a 1-mm gap, matrix size of 256×256, and field of view of 40×40 cm. Images were obtained at 32 time points per slice. DW images were obtained by using a multislice, single-shot, spin-echo echoplanar sequence. Sixteen to 20 slices of 6 mm with a 1-mm gap 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 was varied between 0 and 22 mTm, resulting in 2 to 3 b values of increasing magnitude from 0 to 1000 s/mm.

Image Analysis
Postprocessing of raw DWI and PWI data were performed with the commercial software package Stroketool (Digital Imaging Systems). Isotropic DWI images were obtained by averaging the signal from all orthogonal directions with the highest diffusion weighting (b=1000). Change in MRI transverse relaxivity (DR2*), which is orthogonal directions with the highest diffusion weighting (b=1000). Change in MRI transverse relaxivity (DR2*), which is orthogonal directions with the highest diffusion weighting (b=1000). Change in MRI transverse relaxivity (DR2*), which is orthogonal directions with the highest diffusion weighting (b=1000). Change in MRI transverse relaxivity (DR2*) was plotted on a per-voxel basis over time. A gamma variate function was then fitted to the intensity-time curve on a per-voxel basis. Tmax was calculated with the single-value decomposition method. This technique allows the tissue concentration–time curve to be calculated, on an individual pixel basis, as a deconvolution of the raw contrast-enhanced perfusion images from an arterial input function.13,14 The arterial input function was selected from a branch of the middle cerebral artery contralateral to the infarct. A semiautomated thresholding technique

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Clinical and Imaging Data</th>
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<tr>
<td>Time Window, h</td>
</tr>
<tr>
<td>No.</td>
</tr>
<tr>
<td>Left hemisphere</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Median acute NIHSS (range)</td>
</tr>
<tr>
<td>Mean acute DWI volume, mL (SEM)</td>
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<tr>
<td>Mean acute PWI volume, mL (SEM)</td>
</tr>
<tr>
<td>PWI-DWI mismatch</td>
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<tr>
<td>Clinical-diffusion mismatch</td>
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was used to calculate the volume of tissue with Tmax >4 seconds relative to a comparable region in the unaffected hemisphere.

DWI lesion volumes were measured manually by planimetric techniques. A standard window level was applied to the isotropic images. Volume measurements were determined by investigators blinded to NIHSS scores. PWI and DWI measures were expressed as volumes (mL) and ratios. Interobserver and intraobserver variability of DWI volume measurements in our group has been previously published and is <5%.15

Statistical Analysis
A commercial statistical software package (STATA Corp) was used for statistical analysis. Demographic data are presented as mean values ±SD or median with range. Correlation between nonparametric variables was tested with the Spearman rank-order coefficient. Two-group comparisons were performed with Student’s t test for parametric variables and the Mann-Whitney rank-sum test for nonparametric variables. Linear regression was used to investigate relations between DWI expansion and CDM.

Results

Baseline Clinical Data
A total of 79 patients were included in the study. Mean patient age was 72±10 years. Median time to MRI scan from stroke onset was 5.3 hours (range, 1.5 to 23); 54 patients (64%) were imaged within 6 hours. Median NIHSS and mean DWI and PWI lesion volumes were all larger in the 0- to 6-hour group (Table 1).

Clinical-Diffusion Mismatch
A total of 34 of 79 (43%) patients fulfilled the proposed definition of CDM, and 51 (65%) had PWI-DWI mismatch. In the 54 patients imaged within 6 hours, CDM was present in 22 (41%) and PWI-DWI mismatch in 40 (74%). In the patients studied between 6 and 24 hours, CDM was present in 12 of 25 (48%) and PWI-DWI mismatch in 11 (44%; Table 1).

Acute MRI Lesion Volumes and NIHSS Scores
Acute DWI volume and NIHSS score were not significantly correlated in patients imaged within 6 hours (r=0.21, P=0.13). Between 6 and 24 hours, there was a highly significant positive correlation between DWI volume and NIHSS score (r=0.82, P<0.001). Acute PWI volume was positively correlated with NIHSS score both in the sub-6-hour cohort (r=0.49, P<0.001) and in the 6- to 24-hour cohort (r=0.59, P=0.002). For any given NIHSS score, patients with left-sided lesions had similar PWI volumes compared with those with right-sided lesions (coefficient, −0.81 [−1.64, 0.02], cube-root PWI volume; P=0.055).
In the sub–6-hour cohort, the NIHSS was trichotomized as mild (0 to 7), moderate (8 to 14), and severe (15 to 23) to ascertain whether quantitative information about stroke volume could be inferred from clinical stroke severity as measured by the NIHSS (Figure 1). In the mild category, DWI and PWI volumes were not significantly different ($P=0.5$). However, in the moderate and severe categories, the PWI volume was significantly larger than the DWI volume ($P<0.001$ in both cases). The median DWI and PWI lesion volumes tended to increase with increasing stroke severity, although this was much more prominently seen in the PWI volumes.

### Sensitivity and Specificity Analysis

The sensitivity of CDM (NIHSS $\geq 8$, DWI $\leq 25$ mL) in predicting PWI-DWI mismatch was 55% (95% confidence interval [CI], 40% to 69%), and the specificity was 79% (95% CI, 59% to 92%; Table 2). In sub–6-hour patients, the sensitivity of CDM in detecting PWI-DWI mismatch was 53% (95% CI, 36% to 68%), with a specificity of 93% (95% CI, 64% to 100%) and a correct classification rate of 59% (Figure 2). Altering the definition of CDM changed the test performance characteristics of CDM (Figure 3). Decreasing the DWI cutpoint or increasing the NIHSS threshold resulted in greater specificity at the price of reduced sensitivity. Below a DWI volume of 25 mL, no increase in specificity was achieved with either NIHSS threshold. No combination of a single DWI volume cutpoint and a single NIHSS threshold was both highly sensitive and highly specific. The kappa statistic for agreement between CDM and PWI-DWI mismatch was 0.29 (0.11 to 0.48) for all patients and 0.32 (0.13 to 0.51) for the 0- to 6-hour time window, indicating modest but statistically significant agreement beyond that which would be expected by chance alone.

### DWI Expansion

Subacute MRI scans were used to assess the ability of CDM to predict DWI expansion. The median DWI expansion ratio in patients with subacute DWI expansion was 1.0, with a 95% confidence interval of 0.81 to 1.19. The area under the receiver operating characteristic (ROC) curve for CDM in predicting DWI expansion was 0.85 (0.78 to 0.92).

### Table 2. Sensitivity and Specificity Analysis for CDM as a Test for PWI-DWI Mismatch

<table>
<thead>
<tr>
<th>Time Window</th>
<th>All Patients (n=79)</th>
<th>0–6 Hours (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (95% CI)</td>
<td>55% (40%–69%)</td>
<td>53% (36%–68%)</td>
</tr>
<tr>
<td>Specificity (95% CI)</td>
<td>79% (59%–92%)</td>
<td>93% (66%–100%)</td>
</tr>
<tr>
<td>PPV (95% CI)</td>
<td>82% (65%–93%)</td>
<td>95% (77%–100%)</td>
</tr>
<tr>
<td>NPV (95% CI)</td>
<td>48% (34%–64%)</td>
<td>41% (24%–59%)</td>
</tr>
<tr>
<td>Correctly classified</td>
<td>63%</td>
<td>63%</td>
</tr>
<tr>
<td>Area under ROC curve (95% CI)</td>
<td>0.67 (0.56–0.77)</td>
<td>0.73 (0.62–0.83)</td>
</tr>
</tbody>
</table>

Figure 1. Boxplot describing PWI ($T_{max}+4$ s) and DWI volumes for strokes of increasing severity as categorized by the NIHSS score in patients imaged within 6 hours of symptom onset. For moderate and severe strokes (NIHSS $\geq 8$), median PWI lesion volume is significantly higher than corresponding DWI volume. Both median DWI and PWI lesion volumes tend to increase with increasing stroke severity, but PWI volume is better correlated with NIHSS. *Mann-Whitney rank-sum test.

Figure 2. Scatterplot of DWI lesion volumes vs NIHSS scores for patients imaged within 6 hours of symptom onset. In this cohort, the proposed definition of clinical-diffusion mismatch has a high positive predictive value for perfusion-diffusion mismatch (all but 1 CDM patient also had perfusion-diffusion mismatch).

Figure 3. Plot demonstrating sensitivity and specificity (%) of CDM for perfusion-diffusion mismatch at increasing DWI volume cutpoints and 2 NIHSS thresholds. Specificity declines above a DWI volume of 25 mL. An NIHSS threshold of $\geq 8$ is more sensitive than a threshold of $\geq 12$. A high degree of sensitivity and specificity cannot be achieved with any 1 definition of CDM.
CDM-positive patients (2.3; interquartile range, 1.5 to 5.4) was significantly greater than in CDM-negative patients (1.4; interquartile range, 1.1 to 2.4, P=0.012). A similar degree of DWI expansion was seen in patients with PWI-DWI mismatch (median expansion ratio, 2.3; interquartile range, 1.4 to 5.6; Figure 4). Significant DWI expansion (>20%) was observed in 22 of 22 patients with CDM and in 27 of 28 with PWI-DWI mismatch. Univariate linear regression indicated that CDM was a better predictor of DWI expansion in patients imaged within 6 hours (r²=0.29, P=0.013) relative to those imaged at 6 to 24 hours (r²=0.10, P=0.031).

**Predicting Change in NIHSS**

There was no statistically significant difference in the proportion of patients with early neurologic deterioration (defined as an increase of ≥4 points on the NIHSS at 72 hours) between CDM-positive and -negative patients (2 of 22 vs 5 of 27, P=0.44) and between those with and without PWI-DWI mismatch (2 of 28 vs 5 of 17, P=0.09).

**Discussion**

We found that CDM was present in 41% of our cohort imaged within 6 hours of symptom onset, which is similar to that reported previously. This was significantly lower than the corresponding proportion with perfusion-diffusion mismatch (74%) studied within the same time interval. The presence of CDM predicted PWI-DWI mismatch with high specificity and positive predictive value but only modest sensitivity. Furthermore, CDM also predicted subacute DWI expansion in patients studied within 24 hours after stroke onset.

**MRI Parameters and NIHSS**

The concept of CDM is based on the assumption that the acute NIHSS score is a useful surrogate marker of the total volume of functionally impaired brain tissue, which could potentially replace PWI in the assessment of acute stroke patients. If this assumption is correct, the NIHSS should be more strongly correlated with the acute PWI volume than the DWI volume in patients with PWI-DWI mismatch. Indeed, PWI deficits have been previously reported to be more strongly correlated than DWI lesion volume with acute NIHSS scores. The present study confirms that within 6 hours, wherein a high proportion of patients have PWI-DWI mismatch, acute NIHSS scores are correlated more strongly with PWI than DWI lesion volumes. Thus, the rationale for using acute NIHSS as a surrogate for PWI is supported by our data. There are, however, some caveats: the quantitative relation between NIHSS score and actual perfusion lesion volume is loose, even in this selected patient group. In addition, we excluded patients with brainstem and lacunar syndromes, because correlation of NIHSS score with stroke volume is likely to be poor in the posterior circulation and in lacunar stroke. The NIHSS may also be biased against right hemisphere strokes (systematically underestimating stroke volumes relative to left hemisphere lesions with the same NIHSS score), although we did not observe this in our patient cohort.

**CDM as a Diagnostic Tool**

Specificity (93%) and positive predictive value (95%) within the 6-hour time window appear to be the major strengths of CDM according to the proposed criteria. It is apparent that no single combination of NIHSS threshold and DWI volume cutoff could be both sensitive and specific (Figure 2). Reducing the DWI cutoff to ≤25 mL or increasing the NIHSS threshold to ≥8 does not lead to a useful increase in specificity. It is possible that reducing the NIHSS threshold to ≤8 may lead to improved sensitivity without sacrificing specificity, but there were too few subjects in our cohort with NIHSS scores ≤8 to attempt a meaningful analysis.

The accuracy of CDM as a diagnostic test to predict the presence of perfusion-diffusion mismatch is dependent on the definition of PWI-DWI mismatch. Presently, there is no "gold standard" MRI definition of PWI-DWI mismatch. We selected a definition based on the perfusion parameter Tmax, which is the time to peak MR signal intensity change after deconvolution. It has been shown previously that Tmax+2 seconds and Tmax+4 seconds correlate best with acute NIHSS score. In a recent systematic comparison of PWI-DWI mismatch definitions, we have found that one based on Tmax+4 seconds is a very conservative estimate of the volume of actual tissue at risk. Given the remaining uncertainty of the significance of moderate oligemia (Tmax+2 seconds), we did not include this tissue in our PWI-DWI definition. In fact, doing so would have only resulted in a decrease in the specificity of CDM with no effect on sensitivity.

It is also apparent that the time of assessment affects CDM performance. In our study, the proportion of patients with CDM was higher in the 6- to 24-hour window than in the 0- to 6-hour window. This is not biologically plausible, because CDM should become less frequent with increasing duration of symptoms, in concordance with PWI-DWI mismatch. The poor performance of CDM in predicting PWI-DWI mismatch beyond a 6-hour time window may partially reflect our patient sample. In our study, patients assessed beyond 6 hours had smaller DWI lesion volumes and NIHSS scores compared with those assessed more acutely (although many still fulfilled criteria for CDM). This is consistent with a previous observation that milder strokes tend to present later. As the time from onset increases, these smaller lesions are increasingly likely to represent completed strokes rather than small lesion volumes.
DWI lesions within a larger perfusion abnormality. It may be that a more specific definition may be required if CDM is to be usefully applied beyond a 6-hour time window.

**Prediction of Infarct Expansion**

This study confirms that although CDM appears to have a relatively low sensitivity for detecting PWI-DWI mismatch, the presence of CDM is highly predictive of subsequent expansion of the acute DWI lesion 3 to 5 days after symptom onset. This supports the hypothesis that patients with CDM have tissue that is at risk for infarction but also potentially amenable to salvage, although we note that the subacute MRI scans may overestimate the final infarct volume because of the presence of edema. Overall, our results appear supportive of the original definition of CDM and are consistent with its rationale, because an NIHSS score ≥8 was originally chosen for its association with higher rates of early neurologic deterioration and lower frequency of spontaneous recovery.10,23,24

**Potential Role in Clinical Decision Making**

CDM may be a useful approach for selection of patients for acute stroke therapy, because CDM has now been shown in 2 studies to predict infarct expansion. In addition, our data demonstrate statistically significant agreement between CDM and PWI-DWI mismatch, with very high specificity and positive predictive value. However, CDM is not particularly sensitive for PWI-DWI mismatch, and a recent abstract with a similar study design demonstrated poor agreement between CDM and PWI-DWI mismatch (no better than could be expected by chance).25 We suggest that CDM should be independently prospectively tested as a predictor of response to thrombolysis. Although the PWI-DWI mismatch hypothesis remains unproven at this point, selection for thrombolysis based on CDM (as opposed to PWI-DWI mismatch) would avoid the extra scan time and problems of interpretation associated with PWI.

This study was performed in a highly selected patient population from a single center. The results cannot be generalized to all acute stroke patients. Because this is the second retrospective study to demonstrate an association between CDM and DWI expansion, before routine clinical use the concept of CDM should be tested in a multicenter, randomized, controlled trial of thrombolysis in acute stroke.

**References**

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