A Topographic Study of the Evolution of the MR DWI/PWI Mismatch Pattern and Its Clinical Impact
A Study by the EPITHET and DEFUSE Investigators

Toshiyasu Ogata, MD; Yoshinari Nagakane, MD; Soren Christensen, PhD; Henry Ma, MD; Bruce C.V. Campbell, MD; Leonid Churilov, PhD; Jean-Marc Olivot, MD; Patricia M. Desmond, MD; Gregory W. Albers, MD; Stephen M. Davis, MD; Geoffrey A. Donnan, MD

Background and Purpose—The ischemic penumbra may be classical, with complete annular configuration around the infarct core, or nonclassical with a more fragmented pattern. We tested the hypotheses that these penumbral patterns may be associated with specific predictive factors, influence infarct growth and clinical outcome, and influence the effect of tissue plasminogen activator (t-PA).

Methods—Using the EPITHET/DEFUSE data set, in which patients received alteplase or placebo 3 to 6 hours poststroke, perfusion-weighted imaging and diffusion-weighted imaging images were analyzed. These mismatch patterns were defined as “classical” or “nonclassical.” Multivariate analysis was used to identify variables associated with mismatch patterns, the effect of t-PA, as well as the relationship between mismatch patterns, infarct growth, and clinical outcomes.

Results—We included 158 patients (median age, 74 years; median National Institute of Health Stroke Scale score, 12). Multivariate analysis indicated that the factors associated with classical mismatch pattern type were large mismatch volume (P < 0.001) and cortical infarct location (P = 0.036). Infarct growth, clinical outcome, and the efficacy of t-PA were not statistically different between patterns.

Conclusions—Coregistered mismatch volume and cortical location of infarction were the important factors associated with presence of the classical mismatch pattern. The lack of effect of the type of mismatch patterns on infarct growth, clinical outcomes, or the benefit of t-PA would suggest that mismatch topography is less important during the hyperacute phase of ischemic stroke than during subacute phase. (Stroke. 2011;42:1596-1601.)

Key Words: DWI/PWI mismatch ■ ischemic stroke ■ thrombolysis ■ topographic study

Magnetic Resonance Imaging (MRI) has been used increasingly in acute ischemic stroke imaging. Diffusion-weighted imaging (DWI) provides information about the extent and location of the infarct core, whereas the mismatch between DWI and perfusion-weighted imaging (PWI) is thought to correspond to the ischemic penumbra.1 Traditional depictions of the penumbra have shown the infarct core as located within the ischemic penumbra and surrounded by a rim of penumbral tissue. However, recent reports studied DWI/PWI mismatch patterns of acute stroke patients and found that fragmentation of the mismatch pattern occurred with time up to 48 hours, so that some patients had spatial dissociation of PWI and DWI lesions.2,3 In other words, a portion of the DWI lesion lay outside the associated PWI volume. The classical mismatch pattern was defined as the core of the DWI lesions being completely or mainly confined within the PWI volume, whereas a fragmented pattern was termed nonclassical.2 The classical pattern was predicted by earlier scan time from stroke onset, a larger mismatch volume, superficial middle cerebral artery location, and occlusion of the main trunk of the middle cerebral artery. It is uncertain whether differing mismatch patterns provide prognostic information in the shorter time windows usually available for potential therapeutic intervention. This is particularly so for response to tissue plasminogen activator (t-PA) therapy.

In the phase-2 studies of t-PA therapy, EPITHET4 and DEFUSE5 recruited patients with ischemic stroke between 3 and 6 hours of onset using surrogate MRI parameters as their primary outcome measure. The aggregation of the 2 data sets provides a vehicle to test hypotheses concerning the influence of DWI and PWI topographical relationships. We tested the
hypotheses that these penumbral patterns may: be associated with specific predictive factors, influence infarct growth and clinical outcome, and influence the effect of t-PA.

**Methods**

We used the EPITHET/DEFUSE combined data set, in which patients received alteplase or placebo 3 to 6 hours after stroke onset. The study designs of EPITHET/DEFUSE, including patient eligibility, treatment allocation, and imaging protocol, have been reported previously. Briefly, EPITHET was a prospective double-blind, randomized, controlled, phase-2 trial in which 101 patients received alteplase or placebo 3 to 6 hours after stroke onset. DWI, PWI, and magnetic resonance angiography (MRA) were obtained before treatment and were repeated at 3 to 5 days. T2-weighted images at day 90 were obtained to measure final infarct volume. DEFUSE was a prospective open-label, nonrandomized, multicenter study of 74 consecutive stroke patients treated with t-PA between 3 and 6 hours after symptom onset. DWI, PWI, and MRA, were obtained immediately before and 3 to 6 hours after treatment with alteplase. MRI scans at day 30 included a fluid-attenuated inversion recovery sequence to measure final infarct growth. National Institutes of Health Stroke Scale (NIHSS) score and modified Rankin scale at day 90 were evaluated for the analyses of clinical outcome in both studies. In the 175 patients in the pooled data, we enrolled all patients with DWI, PWI, and accurate coregistrations. DWI, PWI, MRA, and T2-weighted or fluid-attenuated inversion recovery images were also pooled for the analysis. To standardize image analysis, the determination of lesion volume of both DWI and PWI was performed manually by 1 investigator (B.C.). Hypoperfusion lesions were defined as a Tmax delay of 6s or more.

The baseline PWI images were registered on DWI images using Montreal Neurological Institute McGill University tools by 2 investigators (T.O. and Y.N.) blinded to treatment assignment, but not to time point of stroke onset. Automatic registration was used to register baseline PWI to the DWI frame; where this procedure failed, manual landmark-based registration was used to initialize another automatic registration. The quality of coregistration was reviewed by another investigator (S.C.).

Mismatch pattern assessments were performed by 2 independent neuroimaging specialists blinded to clinical details (T.O. and Y.N.) after a calibration was conducted. The classical pattern was defined previously as: the core of the infarct being completely or mainly confined within the perfusion lesion or, in other words, an annular pattern (Figure 1). Other patterns were categorized as nonclassical, usually as a dissociation between DWI and PWI lesion (Figure 2). An inter-rater agreement was calculated.

The volume of initial DWI/PWI mismatch was calculated using the coregistration method previously described (Table 1). This was done to provide a more precise volume than that achieved by simple subtraction of the DWI volume from the PWI volume. The mismatch volume was defined as that of the region of PWI volume that was not overlapped by the DWI volume when they were coregistered.

Analysis of MRA images was performed using the same scoring system as described in the DEFUSE study: major intracranial arteries defined as normal, decreased flow, or occluded. For the purpose of providing a dichotomous measure, arterial findings were categorized as “normal” or “abnormal” (decreased flow or occluded). The location of the DWI infarct core was either superficial or deep middle cerebral artery territory.

**Statistical Analysis**

First, the level of agreement between 2 independent assessors was calculated by weighted kappa score and further validated using Lin's concordance coefficient and reduced major axis regression. To evaluate the difference between the classical and nonclassical patterns, multivariate logistic regression analysis was used. Independent variables were those that showed trend toward being significant in univariate analyses (probability value \( \leq 0.1 \)) and those reported to be significant factors associated with the mismatch patterns in the literature (mismatch volumes, MRI scan time, the presence or absence of vessel occlusion, the location of DWI lesion). Infarct growth and clinical outcomes were compared between the 2 patterns using multivariate logistic regression or median regression analyses (Table 1), adjusting for age, baseline NIHSS score, DWI volume, mismatch volume, abnormal arterial findings, and the administration of alteplase. Finally, we assessed whether efficacy of alteplase was different between the 2 mismatch patterns. Statistical analyses were performed on STATA 10 (STATA Corp.).

**Results**

From a total of 175 patients in the pooled data, we excluded 17 cases (EPITHET, 5; DEFUSE, 12) because of inadequate PWI image or inadequate coregistration. Hence, a total of 158
patients (median age, 75 years; median baseline NIHSS score, 12; interquartile range, 8 to 17) were enrolled in this study. Of these, 133 patients had a follow-up T2 scan at day 90 (EPITHET) or fluid-attenuated inversion recovery at day 30 (DEFUSE), and analyses of infarct growth were performed in the 133 patients. Excellent agreement of the mismatch patterns was achieved between the 2 assessors with kappa score of 0.848 (95% CI, 0.765–0.931), Lin’s concordance correlation coefficient of 0.848 (0.804–0.892). There was no fixed or proportional bias detected by reduced major axis regression (slope $=0.999$; intercept $=0.012$).

Of the 158 patients, 73 patients (46.2%) had a classical mismatch pattern, whereas 85 patients (53.8%) had a nonclassical pattern (Table 2). Patients with a classical pattern tended to be older than those in the nonclassical group (median age 76.0 years compared with 74.0 years; $P=0.096$; Mann-Whitney $U$ test). For baseline characteristics, baseline NIHSS scores were significantly more severe in the classical group compared with in the nonclassical group (median NIHSS, 14 versus 11; $P=0.01$; Mann-Whitney $U$ test).

Logistic regression analysis identified that the factors significantly associated with the mismatch patterns were mismatch volume and location of lesion (Table 3). Abnormal arterial findings were not significantly associated with the mismatch patterns. Despite acceptable variance inflation for the overall regression model, there was a significant correlation between mismatch volume and abnormal arterial finding ($\gamma=0.45; P<0.01$).

Although the univariate analyses indicated that patients with the classical pattern had statistically significant larger infarct growths than those with nonclassical pattern, these statistical significance findings did not hold after adjustment for baseline variables (age, baseline NIHSS score, DWI volume, mismatch volume, arterial abnormality, and administration of alteplase) (Table 4). Also, there were no significant differences between functional and neurological outcomes between the mismatch patterns. There were no significant differences in the effects of alteplase between the mismatch patterns.

**Discussion**

We hypothesized that classical and nonclassical penumbral mismatch topographical patterns may have specific predictive factors, may influence clinical and imaging outcome, and may also have an effect on the benefits of intravenous thrombolysis. By using the EPITHET/DEFUSE combined

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**Table 1. Definitions**

- Co-registered mismatch volume: PWI–wDWI volume
- Volumetric mismatch: PWI–DWI volume
- Infarct growth: expansion between baseline DWI and day-90 T2-weighted lesion (EPITHET) or day-30 FLAIR lesion (DEFUSE)
- Geometric mean: exponential of mean log relative growth
- Relative growth: final lesion volume/baseline DWI lesion volume
- Absolute growth: final lesion volume–baseline DWI lesion volume
- Difference in cube-root volumes: (final lesion volume)$^{1/3}$–(baseline DWI lesion volume)$^{1/3}$
- Any growth: relative growth $>0\%$
- Modified Rankin Scale 0–2
- Modified Rankin Scale 0–1
- Good neurological outcome: NIH Stroke Scale at day 90 of 0 or 1, or improvement $\geq 8$ from baseline
- Reperfusion: $>30\%$ and 10 mL reduction in DEFUSE and $>90\%$ reduction in EPITHET of the hypoperfusion lesion between initial and subacute PWI

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**Figure 2.** Representative case with nonclassical pattern of mismatch. (A) diffusion weighted-image (DWI). B, DWI abnormal lesion (red) and hypoperfusion lesion (green) superimposed on DWI. Note fragmentation of the pattern. C, DWI abnormal lesion and hypoperfusion lesion with brain image (DWI) removed.
data set, we were able to show that the classical pattern of mismatch was associated with larger mismatch volumes in a cortical location. However, the topographical pattern did not influence the clinical or radiological outcomes of thrombolysis, including reperfusion. Based on the penumbral hypothesis, the ischemic core is embedded within a hypoperfused volume. Penumbral tissue can be defined by a region of hypoperfusion without evidence of infarction (DWI signal), and that has the potential to be salvaged by arterial recanalization. However, it has become clear that not all cases have this classical mismatch pattern, whereby the majority of DWI core is surrounded by hypoperfused tissue. Furthermore, reversible components of the DWI lesion have been identified that may be calculated as the percentage of the acute DWI lesions not overlapping with the final infarct on the coregistrated image; however, its extent is debated. Hence, topographical issues addressed by the coregistration method are becoming increasingly important in the evaluation of outcomes in acute ischemic stroke. Once coregistration of DWI and PWI is completed, the visual method we used to dichotomize mismatch patterns was simple and quick. Therefore, if the mismatch patterns predicted the characteristics, outcomes, and efficacy of t-PA, and coregistration was automated, mismatch pattern recognition would be clinically useful.

Interestingly, of the factors associated with the mismatch patterns we identified in our previous report, which involved patients studied up to 48 hours after stroke onset, only cortical location and mismatch volume were predictive in the current study. The loss of time as a factor in our current study is most likely caused by the limited 3- to 6-hour time window in this data set. The lack of significance of large-vessel occlusion in multivariate analysis may have resulted from its close association with mismatch volume. Also, differences such as severity of stroke, method of measuring hypoperfusion lesion, and the treatment might contribute to the results.

The reason why the classical penumbral pattern is more likely to be located cortically is unclear. The veracity of the finding seems likely given that we have found this in both the short (3- to 6-hour) and longer (0- to 48-hour) time-window populations. One possible explanation is that in cases of middle cerebral artery occlusion, the infarct process in the subcortex is usually more advanced than in the cortex because of the depth of ischemia and lack of collaterals in the former. As we found in our ≤48 hours cohort, a more advanced ischemic and reperfused state is more likely to produce a fragmented nonclassical penumbral pattern.

There are a number of factors that are associated with the clinical and imaging outcomes in stroke patients, including age, DWI volume in the acute phase, major vessel occlusion on MRA, NIHSS score, and location of the lesion. Darby et al suggested that the topographical association of the initial DWI lesions and the volume of maximal hypoperfusion may be important in predicting reperfusion after t-PA. Although numbers were small, Olivot et al suggested that baseline mismatch geography had little influence on clinical response to t-PA. Based on our large combined data set, one of the main implications of our study is that mismatch patterns do not influence clinical and imaging outcomes as much as do other factors mentioned earlier. Hence, for time windows up to 6 hours, mismatch pattern is not a useful criterion for
selection of patients for thrombolysis. Hence, it would be more appropriate to choose the patients eligible for thrombolysis based on factors other than mismatch patterns. However, given that greater fragmentation of the classical pattern occurs with time, this statement may not be true for longer time-windows. With a number of trials underway using imaging-based protocols up to 9 hours poststroke, the importance of late mismatch patterns under these circumstances will be able to assessed.

There were several limitations to this study. First, the judgment of mismatch patterns was subjective, although the agreement between assessors was excellent. Olivot et al dichotomized the patients by assessing the proportion overlap of DWI and PWI lesions. This allowed a high level of objectivity in mismatch categorization. Another possible limitation in our study was our definition and threshold of hypoperfusion. Previously we used Tmax >2s in both EPITHET and DEFUSE. However, more recent analyses suggested that Tmax ≥6s accurately reflected the penumbral threshold, so we have incorporated this value in the current study (Christensen S et al, unpublished data).

In conclusion, in this 3- to 6-hour poststroke cohort, coregistered mismatch volume, and infarct location were the important factors associated with classical versus nonclassical mismatch patterns. Differing patterns did not influence infarct growth, clinical outcomes, or the response to t-PA. Hence, when considering patients within 3 to 6 hours of stroke onset, mismatch topography is not a critical factor in patient selection for thrombolysis.

Sources of Funding
This research was supported by the Victorian Government’s Operational Infrastructure Support Program.

Table 4. Outcomes between Classical and Nonclassical Patterns of Mismatch

<table>
<thead>
<tr>
<th>Classical (N=73)</th>
<th>Nonclassical (N=85)</th>
<th>Unadjusted Difference/ Ratio (95% CI)</th>
<th>Odds Ratio</th>
<th>P-Value</th>
<th>Adjusted Difference/ Ratio (95% CI)</th>
<th>Odds Ratio</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Proportion</td>
<td>N</td>
<td>Proportion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geometric mean</td>
<td>60</td>
<td>1.67</td>
<td>73</td>
<td>1.05</td>
<td>1.60 (1.1–2.4)</td>
<td>0.012</td>
<td>1.09 (0.69–1.71)</td>
</tr>
<tr>
<td>Median relative growth</td>
<td>60</td>
<td>1.48</td>
<td>73</td>
<td>1.04</td>
<td>1.51 (1.1–2.1)</td>
<td>0.012</td>
<td>0.99 (0.76–1.29)</td>
</tr>
<tr>
<td>Absolute growth</td>
<td>60</td>
<td>11.1</td>
<td>73</td>
<td>0.08</td>
<td>8.77 (1.2–20.6)</td>
<td>0.026</td>
<td>−1.30 (−11.2–8.6)</td>
</tr>
<tr>
<td>Difference cube–root</td>
<td>60</td>
<td>0.47</td>
<td>73</td>
<td>0.02</td>
<td>0.39 (0.01–0.77)</td>
<td>0.013</td>
<td>−0.02 (−0.55–0.51)</td>
</tr>
<tr>
<td>Any growth</td>
<td>60</td>
<td>43 (72%)</td>
<td>73</td>
<td>37 (51%)</td>
<td>2.46 (1.2–5.1)</td>
<td>0.02</td>
<td>1.42 (0.6–3.5)</td>
</tr>
<tr>
<td>mRS 0–2</td>
<td>73</td>
<td>27 (37%)</td>
<td>85</td>
<td>42 (50%)</td>
<td>0.59 (0.3–1.1)</td>
<td>0.11</td>
<td>1.02 (0.4–2.5)</td>
</tr>
<tr>
<td>mRS 0–1</td>
<td>73</td>
<td>17 (23%)</td>
<td>85</td>
<td>31 (37%)</td>
<td>0.52 (0.3–1.0)</td>
<td>0.067</td>
<td>0.96 (0.4–2.4)</td>
</tr>
<tr>
<td>Good neurological outcome</td>
<td>73</td>
<td>32 (44%)</td>
<td>85</td>
<td>41 (49%)</td>
<td>0.82 (0.4–1.5)</td>
<td>0.53</td>
<td>1.32 (0.6–3.0)</td>
</tr>
<tr>
<td>Reperfusion</td>
<td>67</td>
<td>34 (51%)</td>
<td>71</td>
<td>28 (39%)</td>
<td>1.58 (0.76–3.28)‡</td>
<td>0.23</td>
<td>1.58 (0.67–3.73)</td>
</tr>
</tbody>
</table>

mRS indicates modified Rankin Scale at day 90; CI, confidence interval.
*Median regression analysis.
†Logistic regression analysis.
‡This value should be treated with caution due to limited fit of the regression model.

Disclosures
G.A.D. is a member of the Boehringer Ingelheim, PAION, Servier, and Sanofi-Aventis advisory boards, has accepted honoraria or consultancy payments from, and has had the costs of participating in scientific meetings reimbursed by, Boehringer Ingelheim, Sanofi-Aventis, and Servier. G.A.D. has received grants from Sanofi-Aventis, and grants and consultancy payments from Boehringer Ingelheim. S.M.D. is a member of the PAION, Servier, and Novo Nordisk advisory boards, and has received honoraria for lectures from Novo Nordisk, Sanofi-Aventis, Pfizer, and Boehringer Ingelheim. G.W.A. is a consultant for Genentech and a member of the Steering Committee for Lundbeck.

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