Refining the Perfusion–Diffusion Mismatch Hypothesis

K.S. Butcher, MD, PhD, FRCP(C); M. Parsons, PhD, FRACP; L. MacGregor, MBBS, MmedSc; P.A. Barber, PhD, FRACP; J. Chalk, PhD, FRACP; C. Bladin, PhD, FRACP; C. Levi, FRACP; T. Kimber, FRACP; D. Schultz, FRACP; J. Fink, FRACP; B. Tress, FRACR; G. Donnan, MD, FRACP; S. Davis, MD, FRACP; for the EPITHET Investigators

Background and Purpose—The Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET) tests the hypothesis that perfusion-weighted imaging (PWI)–diffusion-weighted imaging (DWI) mismatch predicts the response to thrombolysis. There is no accepted standardized definition of PWI-DWI mismatch. We compared common mismatch definitions in the initial 40 EPITHET patients.

Methods—Raw perfusion images were used to generate maps of time to peak (TTP), mean transit time (MTT), time to peak of the impulse response (Tmax) and first moment transit time (FMT). DWI, apparent diffusion coefficient (ADC), and PWI volumes were measured with planimetric and thresholding techniques. Correlations between mismatch volume (PWIvol-DWIvol) and DWI expansion (T2day 90-vol-DWIacute-vol) were also assessed.

Results—Mean age was 68±11, time to MRI 4.5±0.7 hours, and median National Institutes of Health Stroke Scale (NIHSS) score 11 (range 4 to 23). Tmax and MTT hypoperfusion volumes were significantly lower than those calculated with TTP and FMT maps (P<0.001). Mismatch ≥20% was observed in 89% (Tmax) to 92% (TTP/FMT/MTT) of patients. Application of a +4s (relative to the contralateral hemisphere) PWI threshold reduced the frequency of positive mismatch volumes (TTP 73%/FMT 68%/Tmax 54%/MTT 43%). Mismatch was not significantly different when assessed with ADC maps. Mismatch volume, calculated with all parameters and thresholds, was not significantly correlated with DWI expansion. In contrast, reperfusion was correlated inversely with infarct growth (R=-0.51; P=0.009).

Conclusions—Deconvolution and application of PWI thresholds provide more conservative estimates of tissue at risk and decrease the frequency of mismatch accordingly. The precise definition may not be critical; however, because reperfusion alters tissue fate irrespective of mismatch. (Stroke. 2005;36:1153-1159.)

Key Words: magnetic resonance imaging, diffusion-weighted ▪ magnetic resonance imaging, perfusion-weighted ▪ thrombolysis

Perfusion-weighted imaging (PWI) and diffusion-weighted imaging (DWI) are being used with increasing frequency in the assessment of acute ischemic stroke. Mismatch between a larger PWI abnormality and a smaller DWI lesion has been postulated to represent the ischemic penumbra, in which tissue is at risk for infarction but also potentially amenable to salvage.1 The only proven acute tissue rescue therapy is thrombolysis.2 Unfortunately, this therapy has not been proven effective beyond 3 hours, although there is some evidence that individual patients may respond to reperfusion strategies up to 6 hours after symptom onset.3

The Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET) is designed to test the hypothesis that PWI-DWI mismatch is predictive of the response to thrombolysis 3 to 6 hours after symptom onset. Specifically, it is hypothesized that patients with PWI-DWI mismatch who are treated with tissue plasminogen activator will have reduced expansion of the acute DWI lesion at 90 days.

There is no consensus with respect to what constitutes PWI-DWI mismatch. A wide variety of methods have been used to calculate the presence and degree of mismatch.4–10 In addition, there are several PWI parameters that can be used to determine the region of hypoperfusion. This has been further complicated by the recognition that a portion of the oligemic region does not ultimately infarct and therefore should be excluded from the putative ischemic penumbra.4,5 Finally, standardized models of infarct growth assessment have not yet been established. These are critical questions that must be addressed to test the EPITHET hypothesis. Therefore, we undertook a preliminary analysis of the initial 40 EPITHET

Received February 16, 2005; accepted March 4, 2005.

From the Departments of Neurology (K.S.B., S.D.), Clinical Epidemiology (L.M.), and Radiology (B.T.), Royal Melbourne Hospital, University of Melbourne, Australia; the Department of Neurology, John Hunter Hospital, Newcastle, Australia (M.P., C.L.); the Department of Neurology, Auckland Hospital, New Zealand (P.A.B.); the Department of Neurology, Box Hill Hospital, Melbourne, Australia (C.B.); the Department of Neurology, Royal Adelaide Hospital, Adelaide, Australia (T.K.); the Department of Neurology, Flinders Medical Centre, Adelaide, Australia (D.S.); the Department of Neurology, Christchurch Hospital, New Zealand (J.F.); and the Department of Neurology, Austin Hospital, Melbourne, Australia (G.D.).

Correspondence to Kenneth S. Butcher, Royal Melbourne Hospital, Grattan St, Parkville, Victoria, Australia 3050. E-mail kenthen.butcher@mh.org.au

© 2005 American Heart Association, Inc.

Stroke is available at http://www.strokeaha.org
DOI: 10.1161/01.STR.0000166181.86928.8b

1153
patients. A systematic comparison of commonly used PWI parameters and their effect on mismatch calculations was planned. In addition, we assessed correlations between mismatch and DWI expansion.

**Methods**

**Patients**

Forty patients with acute ischemic stroke were imaged 3 to 6 hours after symptom onset. Patients were prospectively recruited from 9 centers participating in the EPITHET trial. Informed consent was obtained, and local human research committees approved the protocol.

**Imaging Protocol**

Computed tomography (CT) scans were obtained before MRI. Patients with intracranial hemorrhage or ischemic changes in more than one third of middle cerebral artery territory were excluded. MRI scans were obtained with 1.5-T echo-planar imaging (EPI)–equipped scanners (GE Signa/Siemens Vision/Symphony/Philips Intera). Studies were completed at baseline, 3 to 5 (DWI and PWI) and 90 days (T2) after symptom onset.

Perfusion-weighted images were obtained using a bolus of gadolinium di-ethylentetriamine penta-acetic acid (Gd-DTPA; 0.2 mmol/kg), injected at 5 mL/s, followed by 15 mL saline. Twelve-16 slices (32 to 50 time points) were obtained. Slice thickness was 5 to 6 mm +1 mm gap, matrix sizes were 128×128/256×256, and field of view 40×40 cm. Diffusion-weighted images were obtained with single-shot spin-echo EPI sequences. Sixteen to 20 slices 5 to 6 mm +1 mm gap were obtained. Matrix size was 128×128/256×256, FOV was 40×40 cm, and repetition time/echo time 6000/107 ms. Diffusion gradient strength was varied between 0 and 22 mT/m, resulting in b values of 0, 500, and 1000 s/mm.

**Data Analysis**

Postprocessing of raw perfusion images was performed centrally by a single investigator using the software package Stroketool (DIS). This software was used to plot the change in MRI transverse relaxation, which is linearly related to Gd-DTPA concentration, on a per-voxel basis over time. Semiquantitative perfusion maps including time to peak (TTP) and first moment transit time (FMT) were calculated from this tissue response curve. Mean transit time (MTT), relative cerebral blood flow (rCBF), and Tmax maps were normalized to a value of 22 mL/100 g per minute in the centrum semiovale contralateral to the DWI lesion. The hypoperfused volume was then calculated from the number of voxels with rCBF ≤18 mL/100 g per minute, as described previously.

**Statistical Analysis**

Analysis was performed using statistical software (Stata Corporation). Two-way repeated-measures ANOVA and post hoc Tukey’s tests were used to assess the influence of parameter and thresholds on apparent PWI abnormality volume. This required a cube root transformation of the volumes, which were not normally distributed. Correlations between mismatch and DWI expansion volumes were assessed with Spearman’s test. Expansion volume differences were tested with the rank sum test.

**Results**

**Baseline Data**

Thirty-nine patients were included in this analysis. A single patient with no PWI data was excluded. The majority of the patients experienced anterior circulation cortical syndromes. Three patients had posterior circulation strokes, 2 of which were subcortical. Mean patient age was 68±11 years, and median baseline NIHSS was 11 (range 4 to 23). Mean time to CT was 3.3±1.1 hours, and median ASPECTS score was 8.5±3. Mean times to initial, subacute, and final MRI studies were 4.4±0.8 hours, 3.8±1.4 days, and 98±31 days, respectively. Patients were imaged within 1 week of the 90-day target, with 1 exception.

**DWI, ADC, and Outcome T2-Weighted Images**

Median volume of hyperintense lesions on isotropic DWI images was 31.5 (interquartile range [IQR], 16.0, 59.6) mL. Median volume of tissue with ADC ≤80% was 25.9 (IQR, 17.2, 52.8) mL, which was not significantly different from the DWI lesion volumes (P=0.865). Median subacute DWI lesion volume was 55.7 (IQR, 20.9, 198.7) mL (n=36).

---

**TABLE 1. Acute PWI Volumes**

<table>
<thead>
<tr>
<th>PWI Volume</th>
<th>TTP</th>
<th>FMT</th>
<th>Tmax</th>
<th>MTT</th>
<th>Tmax (AIF)</th>
<th>MTT (AIF)</th>
<th>rCBF ≤18 mL/100 g per minute</th>
</tr>
</thead>
<tbody>
<tr>
<td>0s</td>
<td>225.1±125.3</td>
<td>231.5±126.8</td>
<td>180.5±98.4</td>
<td>197.1±105.9</td>
<td>...</td>
<td>...</td>
<td>71.4±64.7</td>
</tr>
<tr>
<td>+2s</td>
<td>145.7±94.0</td>
<td>153.9±90.7</td>
<td>90.7±63.3</td>
<td>98.0±74.0</td>
<td>83.7±55.6</td>
<td>121.1±88.4</td>
<td></td>
</tr>
<tr>
<td>+4s</td>
<td>115.7±82.0</td>
<td>99.3±98.5</td>
<td>62.4±53.5</td>
<td>55.3±51.5</td>
<td>59.2±52.8</td>
<td>79.9±65.8</td>
<td></td>
</tr>
</tbody>
</table>

*P=0.989* | *P=0.999* | *P=0.184*

Interparameter *P* values refer to adjacent columns where not specified.
Subacutely, ADC ≤80% volumes were calculated in 29 patients. In 7 patients, accurate ADC values could not be calculated at the subacute time point because of petechial hemorrhage (n=2), patient movement (n=1), or incomplete data (n=4). In these 29 patients, median subacute ADC ≤80% volume was 37.6 (IQR, 17.4, 86.6) mL, and DWI lesion volume was 54.7 (IQR 13.0, 124.5) mL (P=0.555). At 90 days, median infarct volume as seen on T2-weighted images was 34.7 (IQR, 9.1, 107.3) mL (n=29).

Perfusion-Weighted Images
Visible PWI deficits were present in 37 patients. Mean volume of hyperintense voxels on TTP and FMT maps was 225.2±125.3 mL and 231.5±126.8 mL, respectively. The volumes obtained with these PWI parameters were significantly greater than those seen on maps calculated using deconvolution: Tmax=180.5±98.4 mL and MTT=197.1±105.9 mL (P<0.001; Table 1). Normalization to the contralateral hemisphere +2s and +4s reduced the apparent PWI abnormality volumes consistently for all parameters (Figure 1; Table 1). There were no significant differences between volumes normalized to the contralateral hemisphere and the AIF for Tmax (P=0.947) or MTT (P=0.484). The mean volume ≤18 mL/100 g per minute on normalized rCBF maps (71.4±64.7 mL) was intermediate to that calculated with the time domain parameters at thresholds of +2s and +4s (Table 1).

MTT maps often demonstrated regions of 0 pixel intensity, where transit time could not be calculated. This pattern occurred in 11 of 37 patients with PWI deficits. Voxels in which MTT could not be calculated corresponded to regions where the tissue response curve had not recovered to baseline before scan completion (Figure 2).

PWI-DWI Mismatch
Assessed as a binary variable, defined as PWIvol−DWIvol/DWIvol×100>20%, mismatch was present in 33 of 37 (89%; Tmax) to 34 of 37 patients (92%; TTP/FMT/MTT). Normalization to the contralateral hemisphere +2s reduced the frequency of mismatch to 27 of 37 (73%; TTP and Tmax), 29 of 37 (78%; FMT), and 25 of 37 (68%; MTT). Application of the +4s threshold did not result in a change in the number of patients with >20% mismatch on TTP maps. The +4s threshold further reduced the frequency of mismatch by this definition assessed with Tmax (20 of 37; 54%), FMT (25 of 37; 68%), and MTT maps (16 of 37; 43%).

Figure 1. PWI maps demonstrating hypoperfused volumes in the right hemisphere decrease with application of +2s and +4s thresholds and DWI and ADC maps. The patient initially appears to have PWI-DWI mismatch, but this is not the case after thresholds are applied. Units are s (TTP) and one-tenth s (FMT, impulse residue TTP; Tmax and MTT). A indicates threshold relative to contralateral hemisphere; B, threshold relative to AIF.

Figure 2. Example of failure of MTT calculation when derived from ratio of area under the response curve to its peak (black voxels). Tmax (TTP intensity change; arrow) is not derived and can always be determined.
Prediction of DWI/ADC Expansion

Larger mismatch volumes appeared to be associated with greater DWI expansion (Figure 3). Mismatch volumes calculated with raw PWI maps tended to overestimate the extent of DWI expansion at 90 days. In contrast, mismatch volumes calculated using PWI maps with a +4s threshold underestimated the final volume change in some patients (Figure 3). Mismatch volumes by any definition were not significantly correlated with subacute or outcome DWI expansion (Table 2). Correlation coefficients did not vary with the threshold used to define the mismatch volume. Similarly, expansion of the ADC ≤80% volumes between the acute and subacute time points was not significantly correlated with mismatch defined with ADC and any combination of PWI volumes (ρ[Tmax]=0.36; P=0.055; Figure 4).

Major reperfusion, defined as >90% reduction in the volume of the Tmax abnormality subacutely, was present in 21 patients. Reperfused (median 22.3 [IQR, 12.9, 40.8] mL) and nonreperfusion (35.1 [IQR, 17.3, 63.2] mL) patients were matched for baseline DWI volume (P=0.322). Reperfusion was correlated inversely with DWI expansion subacutely (P<0.0001) and at 90 days (P=0.009). Reperfusion attenuated DWI expansion at both time points, irrespective of mismatch by any definition. Median subacute DWI expansion in reperfused and nonreperfused patients was 3.9 (IQR, 3.6, 13.9) mL and 42.8 (IQR, 10.2, 93.8) mL (P=0.004), respectively (Figure 4). Similarly, median subacute DWI expansion in reperfused and nonreperfused patients was −4.0 (IQR, −11.7, 2.0) mL and 44.2 (IQR, 12.9, 79.2) mL (P<0.001), respectively. At 90 days, the change from initial DWI volume was −8.4 (IQR, 18.9, −0.9) mL in reperfused patients and 27.7 (IQR, −2.8, 52.6) mL in nonreperfused patients (P=0.016). Attenuation of DWI/ADC expansion was seen in nonmismatch as well as mismatch patients (Figures 3 and 4).

Given the strong effect of reperfusion, the relationship between mismatch volumes and DWI expansion was assessed separately in the nonreperfused patients. In this subgroup, mismatch volumes appeared to be more closely correlated with DWI expansion at 90 days, although the relationship was not statistically significant for any PWI parameter (ρ[Tmax]=0.43, P=0.067; and ρ[Tmax +4s]=0.28, P=0.245). The relationship between mismatch volume and DWI expansion in nonreperfused patients has been illustrated by regression lines in Figure 3. Subacute DWI expansion in the nonreperfused subgroup was not correlated significantly with mismatch volume (r[Tmax]=0.31, P=0.197; and r[Tmax +4s]=0.09, P=0.710). These relationships were not altered when subacute expansion was measured as a change in ADC ≤80% volume.

Acute DWI lesion volume was also significantly correlated with subacute DWI expansion but not at 90 days (Table 2).
Larger initial DWI lesions tended to be associated with little or no mismatch tissue. Despite this, these large lesions increased in volume subacutely (Figure 4). In contrast, subacute expansion of the ADC ≤80% lesion was not correlated with the initial volume (rho=0.30; *P*=0.111).

### Discussion

This is the first systematic comparison of PWI-DWI mismatch definitions and the ability of these patterns to predict infarct expansion. It appears that the PWI parameter used in the mismatch definition is far less important than the threshold chosen to represent “significant” oligemia. In addition, the method used to determine this semiquantitative perfusion threshold does not significantly alter the definition. DWI volumes based on an ADC threshold of ≤80% are similar to those measured manually on isotropic images and do not significantly alter the definition of mismatch. This study has also confirmed that the natural history of hypoperfused tissue is dramatically altered by reperfusion.

### Which PWI Parameter?

Dynamic-susceptibility contrast imaging provides only an estimate of true contrast transit time, which is proportional to tissue perfusion. Estimates based on the tissue response curve, such as TTP and FMT, have been referred to as "pseudomeasures" because the basic assumptions of the central volume theory are not met. Specifically, the contrast injection is not instantaneous. Deconvolution is a mathematical approximation of an instantaneous injection based on an AIF. This technique is dependent on the choice of AIF, and in cases of distal intracranial stenoses, it may still overestimate the true volume at risk. In other cases, in which collateral circulation is extensive, deconvolved parameters may underestimate the true penumbra.

We demonstrated that the volume of apparently hypoperfused tissue calculated with deconvolved parameters is on average lower than that seen on TTP or FMT maps, although this is not always the case (Figure 1). Therefore, deconvolved parameters provide a more conservative estimate of the tissue at risk. Our results also indicate that MTT is prone to error. MTT is derived from the ratio of the area under the impulse response curve (deconvolved tissue response) to its peak amplitude. Accurate calculation of the area requires that MR signal intensity return to baseline during the scan acquisition. In voxels in which transit time is extremely delayed, this does not always occur (Figure 2). The software used in our study assigns a 0 value to these voxels, although other programmers assign a maximum value, on the basis of the assumption that transit time is severely delayed. Although this is likely to be true, it is problematic when semiquantitative analyses and thresholds are applied. In contrast, Tmax is a direct measure of the TTP change of the impulse residue, which can always be measured. In our opinion, this simpler measure is the preferred parameter.

**Which Perfusion Threshold?**

It has been recognized for some time that in general, PWI maps tend to overestimate the volume of tissue at risk for infarction. The probability of infarction increases with the severity of the transit time delay. Prolongation of TTP, MTT, or Tmax by 4 to 6 s has been most closely correlated with the final infarct volume. The probability of infarction increases with the severity of the transit time delay. Prolongation of TTP, MTT, or Tmax by 4 to 6 s has been most closely correlated with the final infarct volume.

![Figure 1](http://example.com/figure1.png)

The modified model of the ischemic penumbra has been developed recognizing this. However, we have shown previously that identification of absolute PWI thresholds for infarction is not possible because they are time dependent. The present data confirm that tissue with minimal transit time delays do not have greater predictive value. Others have suggested a multiparameter approach to defining the Tmax deficit, combining data from rCBF, regional cerebral blood volume (rCBV), and time domain maps. Although these additional parameters likely do improve the accuracy of tissue fate prediction in patients with ideal data, our results indicate that errors in rCBV and MTT estimation are common with conventional dynamic susceptibility contrast techniques (Figure 2). Therefore, for the moment, we advocate the use of simple and direct PWI parameters such as Tmax, recognizing that these are only estimates of the tissue at risk.

### Table 2: Univariate Predictors of DWI Expansion

<table>
<thead>
<tr>
<th></th>
<th>Days 3 to 5</th>
<th>Day 90</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>R</em></td>
<td><em>P</em></td>
</tr>
<tr>
<td>Reperfusion</td>
<td>−0.61</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Acute DWI volume</td>
<td>0.38</td>
<td>0.023</td>
</tr>
<tr>
<td>TTP mmv</td>
<td>0.21</td>
<td>0.215</td>
</tr>
<tr>
<td>TTP +2s mmv</td>
<td>0.09</td>
<td>0.616</td>
</tr>
<tr>
<td>TTP +4s mmv</td>
<td>0.06</td>
<td>0.721</td>
</tr>
<tr>
<td>FMT mmv</td>
<td>0.18</td>
<td>0.289</td>
</tr>
<tr>
<td>FMT +2s mmv</td>
<td>−0.04</td>
<td>0.822</td>
</tr>
<tr>
<td>FMT +4s mmv</td>
<td>−0.09</td>
<td>0.581</td>
</tr>
<tr>
<td>Tmax mmv</td>
<td>0.31</td>
<td>0.197</td>
</tr>
<tr>
<td>Tmax +2s mmv</td>
<td>0.14</td>
<td>0.550</td>
</tr>
<tr>
<td>Tmax +2s AIF mmv</td>
<td>0.16</td>
<td>0.359</td>
</tr>
<tr>
<td>Tmax +4s mmv</td>
<td>0.09</td>
<td>0.710</td>
</tr>
<tr>
<td>Tmax +4s AIF mmv</td>
<td>0.14</td>
<td>0.407</td>
</tr>
<tr>
<td>MTT mmv</td>
<td>0.14</td>
<td>0.422</td>
</tr>
<tr>
<td>MTT +2s mmv</td>
<td>−0.20</td>
<td>0.235</td>
</tr>
<tr>
<td>MTT +2s AIF mmv</td>
<td>−0.14</td>
<td>0.392</td>
</tr>
<tr>
<td>MTT +4s mmv</td>
<td>−0.23</td>
<td>0.177</td>
</tr>
<tr>
<td>MTT +4s AIF mmv</td>
<td>−0.10</td>
<td>0.550</td>
</tr>
<tr>
<td>rCBF 18 mmv</td>
<td>0.07</td>
<td>0.683</td>
</tr>
</tbody>
</table>

mmv indicates mismatch volume.

**TABLE 2. Univariate Predictors of DWI Expansion**

Although we found rCBF volumes ≤18 mL/100 g per minute were comparable to Tmax +4s, they did not have greater predictive value. Others have suggested a multiparameter approach to defining the PWI deficit, combining data from rCBF, regional cerebral blood volume (rCBV), and time domain maps. Although these additional parameters likely do improve the accuracy of tissue fate prediction in patients with ideal data, our results indicate that errors in rCBV and MTT estimation are common with conventional dynamic susceptibility contrast techniques (Figure 2). Therefore, for the moment, we advocate the use of simple and direct PWI parameters such as Tmax, recognizing that these are only estimates of the tissue at risk.
Modeling Infarct Growth

It would be ideal to assess infarct growth as a function of mismatch volume as continuous variables. Unfortunately, the distribution of volumes in our cohort and others is not normal. Although normalization of the data with a cube root transformation is possible, our results also indicate that expansion is not constant for all initial DWI volumes, making linear regression invalid. Although nonlinear multivariate modeling is possible, we feel conservative nonparametric tests are best suited to assess the influence of mismatch on infarct growth.

The influence of acute DWI volume on expansion appears to vary with the time of subsequent imaging (Table 2). Subacutely, larger DWI lesions are associated with a disproportionate increase in volume, which is not evident at 90 days. This likely reflects edema, which is maximal at the time of our subacute images (days 3 to 5) and exceeds the volume of the final infarct (Figure 4). Expansion of the bioenergetically compromised region within the first week can also be assessed as growth in the volume of tissue with decreased ADC values. ADC maps are not susceptible to the T2 effects of subacute edema as the raw diffusion images are. Application of an ADC threshold also provides a more objective measure of infarct growth. In the present study, subacute ADC expansion was not related to the acute ADC volume. This suggests ADC maps reflect subacute expansion more accurately than DWI hyperintensities. Despite this, the relationship to mismatch volume is identical for DWI and ADC expansion.

Effect of Reperfusion

We confirmed the previous finding that subacute reperfusion attenuates DWI/ADC expansion relative to those patients with persistently occluded blood flow. The effect of reperfusion is evident despite the fact that we have no information regarding duration of hypoperfusion. This supports the concept that reperfusion strategies are likely to be beneficial 3 to 6 hours after symptom onset. The benefits of reperfusion are not related to mismatch volume (Figure 3), reinforcing the fact that the mismatch hypothesis is unproven. To date, nonmismatch patients have not been assessed adequately to exclude the possibility that they may also benefit from thrombolysis in this time window.

Implications for Ongoing Trials

Our goal was the identification of an optimal PWI-DWI mismatch definition that could be used to test hypotheses in ongoing MRI-based trials including EPITHET, DEFUSE (DWI Evolution For Understanding Stroke Etiology), ROSIE (Reopro-Reteve Reperfusion of Stroke Imaging Evaluation), and DIAS (Desmoteplase in Acute Stroke). Logically, all definitions should be assessed for their ability to predict the response to thrombolysis. Although this will be done, an a priori definition is desirable. We have chosen a deconvolved parameter only because this is theoretically most consistent with the central volume theorem. Application of a threshold not only removes benign oligemic regions from the mismatch region but also provides a more objective measure-
ment. This is relevant because lesion volume assessment on raw PWI maps has been shown to be subject to high inter-rater variability. 10 Although thresholds relative to the contralateral hemisphere or the AIF provide similar results, the latter requires less operator input, which may improve reliability. On the basis of these preliminary results, we therefore propose to use the Tmax +2s definition in the primary EPITHET analysis.

This study has a number of limitations. The true natural history of mismatch tissue cannot be determined from this blinded data set in which approximately half the patients received thrombolysis. However, we would submit that our results and those of others11 indicate that the effects of reperfusion must be considered even in an untreated population. Not all possible definitions of mismatch have been assessed because other methods of determining PWI volumes exist. These include determination of the AIF from peri-infarct arteries and arrival time–insensitive deconvolution techniques.16,23

Conclusions
The presence and degree of mismatch varies considerably with the definition, particularly the PWI threshold used. Mismatch is common 3 to 6 hours after stroke symptom onset. Although reperfusion limits DWI expansion, identification of a mismatch definition that predicts the response to thrombolysis must await the final EPITHET analysis.

Acknowledgments
The EPITHET trial is supported by the National Health and Medical Research Council of Australia as well as an unrestricted research grant from Boehringer Ingelheim, Australia. K.S.B. has been supported by fellowships from the Canadian Institute of Health Research and Alberta Heritage Foundation for Medical Research.

References
Refining the Perfusion–Diffusion Mismatch Hypothesis
for the EPITHET Investigators

Stroke. 2005;36:1153-1159; originally published online May 12, 2005;
doi: 10.1161/01.STR.0000166181.86928.8b
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/36/6/1153

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/