Refining the Definition of the Malignant Profile
Insights From the DEFUSE-EPITHET Pooled Data Set

Michael Mlynash, MD, MS; Maarten G. Lansberg, MD, PhD; Deidre A. De Silva, MBBS, MRCP, FAMS; Jun Lee, MD; Soren Christensen, PhD; Matus Straka, PhD; Bruce C.V. Campbell, MBBS, BMedSc, FRACP; Roland Bammer, PhD; Jean-Marc Olivot, MD, PhD; Patricia Desmond, MSc, MD, FRANZCR; Geoffrey A. Donnan, MD, FRACP; Stephen M. Davis, MD, FRACP; Gregory W. Albers, MD; on behalf of the DEFUSE-EPITHET Investigators

Background and Purpose—To refine the definition of the malignant magnetic resonance imaging profile in acute stroke patients using baseline diffusion-weighted magnetic resonance imaging (DWI) and perfusion-weighted magnetic resonance imaging (PWI) findings from the pooled DEFUSE/EPITHET database.

Methods—Patients presenting with acute stroke within 3 to 6 hours from symptom onset were treated with tissue plasminogen activator or placebo. Baseline and follow-up DWI and PWI images from both studies were reprocessed using the same software program. A receiver operating characteristic curve analysis was used to identify Tmax and DWI volumes that optimally predicted poor outcomes (modified Rankin Scale 5–6) at 90 days in patients who achieved reperfusion.

Results—Sixty-five patients achieved reperfusion and 46 did not reperfuse. Receiver operating characteristic analysis identified a PWI (Tmax $>$ 8 s) volume of $>$ 85 mL as the optimal definition of the malignant profile. Eighty-nine percent of malignant profile patients had poor outcome with reperfusion versus 39% of patients without reperfusion ($P = 0.02$). Parenchymal hematomas occurred more frequently in malignant profile patients who experienced reperfusion versus no reperfusion (67% versus 11%, $P < 0.01$). DWI analysis identified a volume of 80 mL as the best DWI threshold, but this definition was less sensitive than were PWI-based definitions.

Conclusions—Stroke patients likely to suffer parenchymal hemorrhages and poor outcomes following reperfusion can be identified from baseline magnetic resonance imaging findings. The current analysis demonstrates that a PWI threshold (Tmax $>$ 8 s) of approximately 100 mL is appropriate for identifying these patients. Exclusion of malignant profile patients from reperfusion therapies may substantially improve the efficacy and safety of reperfusion therapies.

Clinical Trial Registration Information—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00238537.

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Key Words: acute stroke $\blacksquare$ DWI $\blacksquare$ PWI $\blacksquare$ MRI $\blacksquare$ thrombolysis $\blacksquare$ tPA $\blacksquare$ reperfusion

It is well-established that the benefit of intravenous thrombolysis for treatment of acute ischemic stroke declines with longer onset-to-treatment times.1 Regression of the ischemic penumbra over time is the predominant hypothesis to explain this decline; however, reperfusion injury and hemorrhage may also contribute. Early reperfusion following ischemic stroke can cause additional injury to the ischemic arterial wall and microvasculature, leading to cerebral edema and brain hemorrhage.2 Although the risk factors for reperfusion injury have not been well-established, it has been hypothesized that patients with large volumes of severely ischemic tissue are at greatest risk.3 Support for this hypothesis has been provided by both the DEFUSE4 and EPITHET5 trials.

The malignant profile was first described by the DEFUSE group as a magnetic resonance imaging (MRI) pattern associated with symptomatic intracranial hemorrhage and poor outcome following reperfusion.4 Criteria for the malignant profile were empirically defined as a baseline lesion on diffusion-weighted MRI (DWI) $>$ 100 mL and/or a lesion on...
perfusion-weighted MRI (PWI) of >100 mL using Tmax delay of >8 seconds. In the EPITHET study, 5 patients with the malignant profile had greater infarct growth, lower frequency of reperfusion, and were less likely to have good neurological and functional outcomes compared with patients who did not have the malignant profile.

These data suggest that excluding malignant profile patients may improve outcomes in clinical trials that are evaluating the efficacy of reperfusion therapies. The goal of this study was to attempt to refine the definition of the malignant profile using baseline DWI and PWI findings from the pooled DEFUSE/EPITHET database.

Methods
The design, methodology, and primary results of DEFUSE and EPITHET studies have been previously reported.4,5 Briefly, DEFUSE was a prospective multinational trial. Patients with acute stroke with National Institutes of Health Stroke Scale (NIHSS) score >5 were enrolled if they could be treated with tissue plasminogen activator within 3 to 6 hours after symptom onset. MRI scans, including DWI, PWI, and magnetic resonance angiography, were obtained before treatment and were repeated 3 to 6 hours after initiation of thrombolytic therapy and again at 30 days. EPITHET was a phase II prospective, randomized, double-blind, placebo-controlled, multinational trial with similar entry criteria to those of DEFUSE. Patients were randomized to treatment with intravenous tissue plasminogen activator or with placebo. MRI scans, including DWI, PWI and magnetic resonance angiography, were obtained before treatment and were repeated at days 3 to 5 and again at day 90.

MRI Protocols and Postprocessing
In both studies, DWI images were obtained with b-values of 0 and 1000 s/mm², and dynamic susceptibility PWI images were acquired with gradient-echo imaging after a bolus of intravenous gadolinium. The software used to create the PWI maps differed between studies and resulted in systematic differences in PWI volumes.6 In addition, the criteria used for identification of DWI lesions also differed. Therefore, we uniformly reprocessed all DWI and PWI images from both studies using the same methodology. We used an in-house developed software package called RAPID (Rapid Analysis of Perfusion Imaging Data).7

In this study, the DWI lesion was defined by RAPID as pixels with apparent diffusion coefficient values below 615/H11022 1000 s/mm², and dynamic susceptibility PWI images were acquired with gradient-echo imaging after a bolus of intravenous gadolinium. The software used to create the PWI maps differed between studies and resulted in systematic differences in PWI volumes.6 In addition, the criteria used for identification of DWI lesions also differed. Therefore, we uniformly reprocessed all DWI and PWI images from both studies using the same methodology. We used an in-house developed software package called RAPID (Rapid Analysis of Perfusion Imaging Data).7

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Definition of Reperfusion
The prespecified thresholds for defining reperfusion used in the original study design of each trial were applied. For DEFUSE patients, reperfusion was defined as a >30% reduction in volume of Tmax>6 s on the 3 to 6 hours follow-up scan. For EPITHET patients, a >90% reduction in volume of Tmax>6 s was required on the 3 to 5 day scan. To achieve early reperfusion, at least a 10 mL reduction in PWI lesion volume was required for all patients.

Assessment of Brain Hemorrhage
Hemorrhagic transformation/parenchymal hematoma was adjudicated by a blinded committee (EPITHET) or a neuroradiologist (DEFUSE) as part of the primary data analysis for each of the individual studies using European Cooperative Acute Stroke Study criteria.9 The original adjudications from each study were used for this analysis.

Optimal Identification of the Malignant Profile
A receiver operating characteristic (ROC) curve analysis was used to identify PWI and DWI volumes that optimally predicted poor outcomes (modified Rankin scale 5–6) at 90 days in patients who achieved reperfusion. Patients who did not have a technically adequate baseline DWI and PWI were excluded. Patients with baseline Tmax>6 s volumes <10 mL were also excluded because, by definition, they could not achieve reperfusion.

Optimal PWI volume thresholds were compared with the optimal DWI volume threshold to identify the single parameter that best defined the malignant profile. To assess whether combinations of DWI and PWI volume thresholds were superior to single parameter definitions, ROC curves were created from probability functions derived from logistic regression analyses using both PWI and DWI volumes as independent predictors.

To determine whether the parameter chosen to define the malignant profile was an independent predictor of poor outcomes, a multivariate analysis was performed. The analysis was first performed for the entire group of patients, then subsequently for patients in whom reperfusion status could be assessed. Finally, an analysis was performed to identify any parameter in which the interaction term between that variable and reperfusion was significantly associated with poor outcome. Any interaction between reperfusion status and study (DEFUSE versus EPITHET) was also assessed.

Statistical Analysis
Continuous variables were compared using Student t test or Mann-Whitney U test. Categorical data were analyzed using χ² or Fisher exact test. Related proportions were compared using McNemar test. The optimal PWI or DWI volume limits for the ROC analysis were prespecified to be able to predict poor outcome with specificity of at least 0.95 (ie, with a minimal possible false-positive rate). For volumes that achieved this degree of specificity, the optimal volume cut-off was identified based on maximizing sensitivity. Odds ratios for poor outcome with the malignant versus non-malignant profiles were estimated for the reperfused and not reperfused groups of patients and were compared using Breslow-Day statistic. The criterion for entering a variable into the multivariate logistic regression analysis was significance at α=0.1 in univariate analysis. We used a backward stepwise procedure to remove variables from the model. All tests were 2-tailed, and statistical significance was defined at α<0.05.

Results
One hundred seventy-five patients were enrolled in DEFUSE and EPITHET studies. Of these, 1 patient withdrew consent, and 63 patients were excluded from the ROC analysis because of inability to determine reperfusion status; in the latter group, 34 patients had technically inadequate baseline and/or post-treatment PWI scans, and 29 patients had a small PWI lesion at baseline. Sixty-five patients achieved reperfusion and 46 patients did not reperfuse. There was no difference in the rate of poor outcome between placebo and tissue plasminogen activator (23% versus 25%, P=0.737). Baseline characteristics are shown in the Table 1.
For the prespecified primary PWI analysis (Tmax > 8 s), the ROC analysis (Figure) identified a volume of >85 mL as the optimal definition of the malignant profile. Using this criterion to define the malignant profile, 27 of 111 patients (24%) with known reperfusion status qualified as malignant. This threshold predicted poor outcome with high true-positive rate in the group of patients who reperfused (Table 2) and provided good differentiation from the group of patients who did not reperfuse; in the reperfused versus not reperfused groups, 8 of 9 patients (89%) versus 7 of 18 patients (39%) had a poor outcome (P=0.019). In contrast, among patients without the malignant profile, there was a trend for reperfusion to be associated with a smaller chance of poor outcome: 5 of 56 patients (9%) had poor outcome in the reperfusion group versus 7 of 28 patients (25%) without reperfusion (P=0.094). The odds ratio for having a poor outcome in optimally defined malignant versus nonmalignant patients was 82 (95% CI, 8.4–1036) versus 1.9 (95% CI, 0.5–6.8) in patients who did not reperfuse (P=0.002). When adjusted for treatment with tissue plasminogen activator versus placebo, these ORs were 94 (8.5–1036) versus 2.5 (0.6–10), respectively. The analyses performed using Tmax > 6 s and Tmax > 10 s thresholds identified volumes of >120 mL and >65 mL as optimal (Table 2).

The DWI analysis identified a volume of 80 mL as optimal; however, this threshold was less sensitive (0.23) compared with the PWI threshold (0.62; P=0.06). The overall performance of DWI to predict outcome was less accurate when compared with PWI, although the difference was not statistically significant; areas under the curve were 0.66 versus 0.82, P=0.203. No combination of DWI and PWI thresholds performed better than PWI alone (Figure).

The baseline magnetic resonance angiography was of adequate technical quality for analysis in 22 of 27 patients identified as malignant based on the optimized definition. A complete internal carotid artery occlusion was present in 12 patients, and partial internal carotid artery occlusion present in 2 patients; the other 8 patients had either a complete (n=6) or partial (n=2) M1 occlusion. Among the malignant patients who reperfused, 67% developed a parenchymal hematoma (either a PH1 or PH2) on an early follow-up scan. In contrast,
among the nonreperfusers, only 11% developed a parenchymal hematoma (all PH1; \( P/H_1 = 0.006 \)).

Among patients with the malignant profile, baseline characteristics were similar between those who reperfused versus those who did not reperfuse (Table 3). Baseline volume of \( \text{Tmax} > 8 \text{s} \) \( > 85 \text{mL} \) was verified to be an independent predictor of poor outcome among all patients (Table 4); other independent predictors of poor outcome were older age and higher baseline NIHSS. The only predictor of poor outcome that had a significant interaction between the “parameter times reperfusion” was baseline volume of \( \text{Tmax} > 8 \text{s} \) \( > 85 \text{mL} \); adjusted for age, this was a powerful independent predictor of poor outcome in patients who reperfused \( (\text{OR} = 78.6 \ [3.2 \text{ to } 1937]; \ P/\text{OR} = 0.039 \text{ for interaction factor with reperfusion status}) \), but was not significantly predictive of poor outcome in the non-reperfused patients \( (\text{OR} = 4.2 \ [0.86 \text{ to } 20.4]; \ P = 0.077) \). There was no interaction between reperfusion status and study group (DEFUSE versus EPITHET).

### Table 2. Malignant Lesion Definitions and Their Efficacy for Prediction of Poor Outcome (mRS 5–6 at 90 d)

<table>
<thead>
<tr>
<th>Malignant Lesion Definition</th>
<th>Reperfusion Status</th>
<th>Sensitivity, (95% CI)</th>
<th>Specificity, (95% CI)</th>
<th>Positive Predictive Value (95% CI)</th>
<th>Odds Ratio</th>
<th>( P ) of Odds Ratio Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{DWI} &gt; 80 \text{mL} )</td>
<td>Positive</td>
<td>0.23 (0.06–0.54)</td>
<td>0.98 (0.88–0.999)</td>
<td>0.75 (0.22–0.99)</td>
<td>15.3 (1.4–162)</td>
<td>0.226</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>0.21 (0.06–0.51)</td>
<td>0.91 (0.74–0.98)</td>
<td>0.50 (0.14–0.86)</td>
<td>2.6 (0.5–15)</td>
<td></td>
</tr>
<tr>
<td>( \text{Tmax} &gt; 6 \text{s} &gt; 120 \text{mL} )</td>
<td>Positive</td>
<td>0.62 (0.32–0.85)</td>
<td>0.98 (0.88–0.999)</td>
<td>0.89 (0.51–0.99)</td>
<td>82 (8.4–792)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>0.43 (0.19–0.70)</td>
<td>0.66 (0.47–0.81)</td>
<td>0.35 (0.15–0.61)</td>
<td>1.4 (0.4–5.2)</td>
<td></td>
</tr>
<tr>
<td>( \text{Tmax} &gt; 8 \text{s} &gt; 85 \text{mL} )</td>
<td>Positive</td>
<td>0.62 (0.32–0.85)</td>
<td>0.98 (0.88–0.999)</td>
<td>0.89 (0.51–0.99)</td>
<td>82 (8.4–792)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>0.50 (0.24–0.76)</td>
<td>0.66 (0.47–0.81)</td>
<td>0.39 (0.18–0.64)</td>
<td>1.9 (0.5–6.8)</td>
<td></td>
</tr>
<tr>
<td>( \text{Tmax} &gt; 10 \text{s} &gt; 65 \text{mL} )</td>
<td>Positive</td>
<td>0.54 (0.26–0.80)</td>
<td>0.98 (0.88–0.999)</td>
<td>0.88 (0.47–0.99)</td>
<td>60 (6.2–570)</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>0.50 (0.24–0.76)</td>
<td>0.72 (0.53–0.86)</td>
<td>0.44 (0.21–0.69)</td>
<td>2.6 (0.7–9.4)</td>
<td></td>
</tr>
</tbody>
</table>

### Discussion

This analysis confirms that patients who have poor outcomes associated with reperfusion can be identified from baseline MRI findings. The original definition of the malignant profile (DWI and/or PWI \( \text{Tmax} > 8 \text{s} \) thresholds of 100 mL) was based on observations from a very small sample of patients.\(^4\) The current analysis affirms that a threshold of approximately 100 mL is appropriate, and suggests that PWI may perform better than does DWI for identification of the malignant profile.

The volume of the severe perfusion deficit \( \text{Tmax} > 8 \text{s} \) \( > 85 \text{mL} \) was an independent predictor of poor outcome in patients who reperfused, but it was not a significant predictor in patients who did not reperfuse. These findings suggest that reperfusion may lead to detrimental effects in this select patient population. An optimized definition of the malignant profile based only on DWI lesion size identified patients who had poor outcomes regardless of whether reperfusion was achieved.

### Table 3. Baseline Characteristics for Malignant Profile Patients: Reperfused Versus Not Reperfused Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Reperfused (N=9)</th>
<th>Not Reperfused (N=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Median, IQR)</td>
<td>82 (80–85)</td>
<td>64 (55–74)</td>
</tr>
<tr>
<td>Sex, female</td>
<td>3 (33)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (67)</td>
<td>13 (72)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (22)</td>
<td>6 (33)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>2 (22)</td>
<td>5 (28)</td>
</tr>
<tr>
<td>History of smoking</td>
<td>3 (33)</td>
<td>10 (56)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3 (33)</td>
<td>6 (33)</td>
</tr>
<tr>
<td>Admission glucose, mg/dL</td>
<td>129 (108–142)</td>
<td>138 (114–222)</td>
</tr>
<tr>
<td>SBP baseline, mm Hg</td>
<td>165 (125–179)</td>
<td>140 (135–154)</td>
</tr>
<tr>
<td>DBP baseline, mm Hg</td>
<td>81 (67–89)</td>
<td>78 (63–90)</td>
</tr>
<tr>
<td>NIHSS baseline</td>
<td>18 (12–22)</td>
<td>17 (14–20)</td>
</tr>
<tr>
<td>Time to baseline MRI, min</td>
<td>245 (205–261)</td>
<td>225 (188–280)</td>
</tr>
<tr>
<td>Time to treatment, min</td>
<td>290 (197–310)</td>
<td>276 (240–340)</td>
</tr>
<tr>
<td>Evidence of obstruction on MRA</td>
<td>6 (100)†</td>
<td>16 (100)‡</td>
</tr>
<tr>
<td>Degree of obstruction‡</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>Received IPA</td>
<td>7 (78)</td>
<td>6 (33)</td>
</tr>
</tbody>
</table>

\^Significant at \( \alpha < 0.05 \).

†Not technically adequate in 3 patients.

‡MRA was not technically adequate in 2 patients.

§Degree of obstruction categories: 0, complete occlusion; 1, partial occlusion; 2, normal.
If these findings can be verified prospectively, they will have very important clinical and research consequences. Including patients who have very poor prognostic signs that are independent of reperfusion may dilute the power of a study to establish the benefit of a reperfusion therapy. In contrast, treating patients who are at increased risk of harm from reperfusion can directly offset the benefits of an otherwise effective reperfusion therapy.

PWI findings may be a more sensitive predictor of reperfusion-related injury than are DWI findings because a large and severe PWI lesion may be a better predictor of serious injury to the ischemic arterial wall. Reperfusion of injured microvasculature may cause breakdown of the blood brain barrier, leading to vasogenic edema and potentially to symptomatic hemorrhage. This hypothesis is supported by our finding that parenchymal hematomas occurred significantly more frequently in malignant profile patients who experienced reperfusion compared with those who did not reperfuse. Another reason why the early severe PWI lesions may be more sensitive than are DWI lesions for identification of the malignant patients is that expansion of DWI lesions into areas of severe hypoperfusion evolves over time. Therefore, the early DWI lesion can underestimate the volume of severe hypoperfusion. The EPITHET investigators demonstrated that very low cerebral blood volume is a stronger predictor of the risk of hemorrhagic transformation than is DWI volume. The University of California Los Angeles Samsung Stroke collaborators observed that aggressive treatment and severe hypoperfusion, but not DWI volume, were associated with hemorrhagic transformation.11

In a retrospective study reported by Yoo et al12 among patients undergoing intra-arterial therapy, baseline DWI lesion volume of >70 mL was identified as a threshold to define a futile group. All 6 patients in the futile group had poor clinical outcome (defined as modified Rankin Scale ≥3 at 3 months), including a high mortality rate despite a 50% recanalization rate. These patients also had significantly larger mean transit time PWI lesion volumes.

There are some limitations to our study. Post-treatment MRI scans were performed at different time windows in DEFUSE and EPITHET studies, therefore we were not able to define reperfusion identically for each study population. In addition, reperfusion was ascertained at a relatively late time point in EPITHET. The sample size of malignant profile patients was small, and was particularly small in the subgroup with reperfusion. Because of this limitation, 95% CI for ORs were very wide. The malignant profile patients with reperfusion were older than were the patients who did not achieve reperfusion yet had identical median baseline NIHSS scores. Not all patients could be included in the primary analysis because of a technically inadequate PWI scan at either baseline or early follow-up. We used only 1 apparent diffusion coefficient threshold to identify DWI lesions; however, the threshold used was optimized in a prior study and it produces volumes that are similar to adjacent thresholds.7 Using other apparent diffusion coefficient thresholds or alternative methods for quantifying DWI lesions might yield better results and should be considered for future study. Other considerations for additional research include analyses of the performance of total PWI plus DWI lesion volume or the union of PWI and DWI lesions voxels on coregistered maps.

Conclusions

In conclusion, based on data from the pooled DEFUSE/EPITHET data set, a baseline Tmax>8 seconds PWI lesion >85 mL defines patients who respond unfavorably to reperfusion; they experienced worse clinical outcomes and higher rates of parenchymal hematoma with reperfusion. If validated in prospective studies, exclusion of malignant profile patients from reperfusion therapies may substantially improve the efficacy and safety of reperfusion therapies.

Sources of Funding

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Disclosures
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References
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Abstract

精确定义不佳核磁影像
来自 DEFUSE-EPITHET 合并数据库的观察

Refining the Definition of the Malignant Profile
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背景及目的：通过来自 DEFUSE/EPITHET 数据库的基线弥散加权核磁共振成像 (DWI) 及灌注加权核磁共振成像 (PWI) 的资料，界定急性卒中患者的不佳 MRI 图像。

方法：急性卒中的患者在发病 3-6 小时内分别接受了组织纤溶酶原激活物或安慰剂治疗。使用相同的软件程序处理两组间的基线及随访 DWI 及 PWI 图像。通过受试者操作特征曲线分析计算 Tmax 及 DWI 体积，这两项指标是预测血管再通患者发病 90 天预后不良 (修正后 Rankin 评分 5-6 分)的最佳指标。

结果：65 个患者实现了血管再通，46 个患者没有实现血管再通。根据受试者操作特征曲线发现，基线 PWI (Tmax>8 秒) 体积大于 85 mL 是不佳 MRI 图像的最佳界定值。89% 的 MRI 图像不佳者存在血管再通后预后不良，而没有再通的患者只有 39% 预后不良 (P=0.02)。脑实质血肿更容易发生在 MRI 图像不佳且血管再通的患者，相比没有血管再通者其发生率较低 (67% vs 11%, P<0.01)。DWI 分析发现 80 mL 为最佳 DWI 阈值，但是没有 PWI 敏感。

结论：通过基线 MRI 的检测结果可预测卒中患者经过血管再通治疗后发生脑实质血肿及不良预后的可能性。当前的分析发现 PWI (Tmax>8 秒) 超过 100 mL 可能提示血管再通后预后不良。具有不佳核磁共振影像的患者不进行再通治疗，可以在很大程度上改善再通治疗的有效性和安全性。

关键词：急性卒中；DWI；PWI；MRI；溶栓；tPA；再通

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