Moving Beyond a Single Perfusion Threshold to Define Penumbra
A Novel Probabilistic Mismatch Definition

Yoshinari Nagakane, MD, PhD*; Soren Christensen, PhD*; Toshiyasu Ogata, MD, PhD; Leonid Churilov, PhD; Henry Ma, MBBS; Mark W. Parsons, PhD; Patricia M. Desmond, MD, FRACP; Christopher R. Levi, FRACP; Kenneth S. Butcher, MD, PhD; Stephen M. Davis, MD, FRACP; Geoffrey A. Donnan, MD, FRACP; for the EPITHET Investigators

Background and Purpose—The mismatch lesion volumes defined by perfusion-weighted imaging exceeding diffusion-weighted imaging have been used as a marker of ischemic penumbral tissue. Defining the perfusion lesion by thresholding has shown promise as a practical tool; several positron emission tomography studies have indicated a more probabilistic relationship between perfusion and infarction. Here, we used a randomized controlled trial dataset of tissue-type plasminogen activator 3 to 6 hours after stroke to: (1) quantify the relationship between severity of hypoperfusion (measured by Tmax) and risk of infarction; (2) exploit this relationship to present a novel definition of mismatch based on infarct probabilities rather than dichotomies; and (3) examine the treatment response in the subgroup of patients with mismatch by the new definition.

Methods—Patients from the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) were included. Baseline perfusion-weighted imaging and 90-day T2-weighted imaging were coregistered. Perfusion-weighted imaging lesion volumes were divided into 10 Tmax delay strata, and infarct risk was defined as the fraction of the tissue at a given Tmax strata that progressed to infarction by day 90.

Results—Sixty-two patients were studied. Infarct risk was an increasing function of Tmax for all subgroups, including the whole cohort. The probabilistic approach outperformed all Tmax thresholds, with exception of the Tmax ≥10 threshold, for which it was only favored by a trend.

Conclusions—Infarct risk and treatment effect increased with severity of perfusion abnormalities. This suggests that a severity-weighted mismatch definition may define penumbral tissue more accurately. (Stroke. 2012;43:1548-1555.)

Key Words: magnetic resonance imaging ■ mismatch ■ penumbra ■ perfusion-weighted imaging ■ tissue-type plasminogen activator

Ischemic penumbral tissue is at risk of infarction but has the potential to be salvaged by reperfusion and/or other strategies.1 With the advent of functional MRI techniques, the concept of mismatch defined by perfusion-weighted imaging (PWI) exceeding diffusion-weighted imaging (DWI) lesion volumes was postulated as a penumbral marker.2 Patients with PWI/DWI mismatch are likely to benefit from timely reperfusion and may be eligible for thrombolytic therapy beyond the current therapeutic time window.3 A recent meta-analysis showed that MRI-selected patients treated with thrombolyis beyond 3 hours had improved clinical outcomes with reperfusion/recanalization.4

In acute stroke, PWI is used to estimate the tissue regions that will infarct if hypoperfusion persists and reperfusion is not achieved. Positron emission tomography studies have focused on determining thresholds for the separation between benign oligemia and penumbra, the so-called penumbral thresholds. Based on these findings, several MR studies have aimed at identifying parameters and thresholds that correspond best with this penumbral threshold.5-7 In practice, the hypoperfused at-risk region is most commonly defined as a region above a certain threshold value of mean transit time or time to peak of the residue function (Tmax).8 It is clear that lower threshold values may include significant amounts of

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From the National Stroke Research Institute (Y.N., T.O., L.C., H.M., G.A.D.), Florey Neuroscience Institutes, Austin Health, University of Melbourne, Australia; Department of Neurology (S.C., S.M.D.), Royal Melbourne Hospital, University of Melbourne, Australia; Department of Mathematics and Statistics (L.C.), University of Melbourne, Australia; Department of Neurology (P.M.D., C.R.L.), Hunter Medical Research Institute, John Hunter Hospital, University of Newcastle, Australia; Department of Neurology (K.S.B.), University of Alberta, Edmonton, Alberta, Canada; Department of Radiology (M.W.P.), Royal Melbourne Hospital, University of Melbourne, Australia.

*Y.N. and S.C. contributed equally to this work.

Correspondence to Geoffrey A. Donnan, Florey Neuroscience Institutes, University of Melbourne, Level 2 Alan Gilbert Building, 161 Barry Street, Carlton South Victoria 3053, Australia. E-mail gdonnan@unimelb.edu.au

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by higher Tmax values.

To quantify the relationship between severity of hypoperfusion and risk of infarction, we coregistered the original EPITHET trial day 90 coregistered images to verify correct superposition.

In this study, we used data from a phase II randomized controlled trial of tissue-type plasminogen activator with MRI-based outcome measures to: (1) quantify the relationship between severity of hypoperfusion (as measured by Tmax) and risk of infarction; (2) exploit this relationship to present a novel definition of mismatch based on infarct Tmax severity profile, patient A had larger amounts of very prolonged Tmax (see color codes) than patient B. Patient A had an acute diffusion-weighted imaging (DWI) lesion of 145 mL expanding to 188 mL, whereas patient B presented with a 3-mL DWI lesion expanding to 5 mL on day 90. The severity profile is for all slices, but only 1 representative slice for each patient is shown here.

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Figure 1. Illustrative example of different Tmax lesion profiles. Patients A and B had comparable Tmax ≥2 lesion volumes (229 and 255 mL, respectively); however, when examining the Tmax severity profile, patient A had larger amounts of very prolonged Tmax (see color codes) than patient B. Patient A had an acute diffusion-weighted imaging (DWI) lesion of 145 mL expanding to 188 mL, whereas patient B presented with a 3-mL DWI lesion expanding to 5 mL on day 90. The severity profile is for all slices, but only 1 representative slice for each patient is shown here.

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linear model with patients as a grouping variable. To compare infarct risks by alteplase versus placebo and by recanalization versus no recanalization, multilevel random-effect linear models with appropriate interaction terms and patients as a grouping variable were utilized. As per the original EPITHET analysis protocol, the primary outcome measure (infarct growth attenuation in mismatch patients between alteplase and placebo assessed by a t test for ratio of the geometric means) as well as secondary outcome measures (relative growth, absolute growth, and the difference of cube-root-transformed volume change) were assessed.

Results
Out of 101 patients enrolled in EPITHET, 99 patients had baseline PWI and 72 had both baseline PWI and day 90 T2-weighted imaging (day 92 interquartile range, 90–95). Six patients with parenchymal hematoma and 4 patients with severely distorted EPI imaging were excluded from the assessment of Tmax stratified infarct risk. For the remaining 62 patients (29 received alteplase and 33 received placebo), baseline PWI and day 90 T2-weighted imaging were used for this analysis. Recanalization status could be assessed in 29 patients with adequate pretreatment and posttreatment MRA scans. Of these, recanalization was present in 18 patients. The Table shows baseline characteristics, and there was no significant difference between the alteplase and placebo groups. Also, the baseline risk factors and imaging characteristics did not differ between recanalization and no recanalization groups, except for prevalence of current or past smoking and median DWI lesion volumes.

Infarct Risks in Each Tmax Strata
Figure 2A shows the volume of tissue within specified Tmax strata on baseline PWI and the volume of infarcted tissue within specified Tmax strata on day 90 T2-weighted imaging for all 62 patients. Infarct risks in each Tmax strata increased progressively with the Tmax values (Figure 2B). A strong relationship between the infarct risks and severity of Tmax values was observed (increase of 2.2% per unit of Tmax; 95% CI, 2.0%–2.4%; P<0.001; intraclass correlation coefficient=0.65). The positive relationship between infarct risks and Tmax severity was maintained in subgroups of treatment (Figure 3A) and recanalization status (Figure 3B). Corresponding increases in risk differed significantly between alteplase and placebo subgroups (interaction Tmax by treatment, P<0.001) and between recanalization and no recanalization subgroups (interaction Tmax by recanalization, P<0.001). Patients without recanalization and those treated by placebo had high infarct risks, particularly in severe Tmax strata.

Prediction of Final Lesion Volumes
Figure 4 shows the Tmax versus severity relationships in the 11 patients with no recanalization. To assess the accuracy of infarct volume prediction, we calculated the differences (residuals) between baseline PWI volumes and 90-day infarct volumes for conventional Tmax thresholds in 11 patients with no recanalization (Figure 5A). Low Tmax thresholds, such as ≥2, ≥4, and ≥6 seconds, overestimated the 90-day infarct volumes, whereas high thresholds, such as ≥12 and ≥14, underestimated the same volumes. Tmax thresholds of ≥8 and ≥10 seconds provided the most accurate estimation of the 90-day infarct volumes (median differences of 31 and −35 mL, respectively). The Tmax ≥10 estimates did not differ significantly from the severity-weighted estimate (P=0.2), but all other Tmax estimates showed significantly worse estimation of the final infarct with a maximum P=0.0068. For comparison, we also analyzed the DWI performance, which was outperformed by the severity-weighted prediction (P=0.032).

Severity-Weighted Mismatch Definition
When mismatch was assessed in all EPITHET patients using the severity-weighted predicted infarct volumes generated by the infarct risks in the nonrecanlizated patients, the prevalence of the severity-weighted mismatch was 62% (61/99; Figure 5B). For the EPITHET primary outcome measure, the patients with severity-weighted mismatch showed trends to infarct growth attenuation with alteplase compared with placebo, such as geometric mean (P=0.2681), relative growth (P=0.0716), absolute growth (P=0.0873), and difference in cube-root lesion volume (P=0.0563), although it did not reach statistical significance, perhaps because of the lower number of patients. In comparison, the original EPITHET mismatch definition using the threshold approach with
Tmax ≥ 2 seconds that classified 86% (85/99) of patients with mismatch was also nonsignificant for all analytical methods of infarct growth, such as geometric mean (P=0.239), relative growth (P=0.054), absolute growth (P=0.126), and difference in cube-root lesion volume (P=0.069).

**Discussion**

The present study showed that the risk of infarction increased with the severity of perfusion deficits instead of showing the expected threshold, although across patients Tmax 8 to 10 seconds did exhibit a sharp slope (Figure 3B). The source of this probabilistic relationship appeared to be caused by both intrapatient and interpatient variability in the Tmax–infarct risk relationship. This suggests that no single PWI threshold valid across patients can perfectly distinguish between salvageable tissue and areas destined to infarct (Figure 4). Hence, the mismatch between single PWI thresholds and DWI lesion volumes may provide an oversimplified penumbra estimate. Even so, the calculation of the predicted infarct volume using the severity-weighted probabilistic approach is no more complex than the quantification of a threshold-defined mismatch.

Differentiation of true penumbra from tissue experiencing benign oligemia has been the major challenge to the PWI/DWI mismatch concept.9 In general, the unthresholded visual PWI/DWI mismatch volume is greater than the volume of penumbra defined by positron emission tomography.15–18 Obviously, higher PWI thresholds provide smaller PWI lesion volumes, so using a higher PWI threshold increases specificity, but at the cost of sensitivity. This has been shown in a number of studies, and these findings are consistent with the increasing severity–risk relationship.5,6,19 In our study, Tmax thresholds of ≥8 and ≥10 seconds appeared to best-predict the final infarct volume; however, the best thresholds for final infarction in terms of spatial sensitivity and specificity are likely lower than these numbers.19

![Figure 2. Baseline tissue volume and infarcted tissue volume within specified Tmax strata (A) and infarct risks in each Tmax strata (B) for all patients (n=62). Boxes indicate median in A and interquartile ranges in B. Bars indicate maximum and minimum values, and lines in the boxes and numbers indicate median values.](http://stroke.ahajournals.org/content/96/20/1551/F2.large.jpg)
A model to predict final infarction must be based on patients with no reperfusion. The clinically relevant question is what will happen to the tissue if there is no reperfusion, and this needs to be estimated in patients with no reperfusion. It has to be acknowledged that many patients have reperfusion spontaneously and will never have infarction to an extent predicted by the model. It is likely that further research can help identify this subset of patients by means of occlusion site or other reperfusion determining factors and, in this way, can improve the model for these patients. In the present study, we based the predictive model on patients without recanalization as a proxy for no reperfusion because the best reperfusion definition for this type of study is unknown. Interestingly, the infarct risks did not reach 100%, even for the highest Tmax range in the nonrecanalized group. We speculate that factors such as collateral supply in some cases inflate Tmax and do not cause infarction, which is consistent with recent findings that Tmax reflects a combination of hemodynamic effects. Visual inspection indicated that regions close to sinuses and edges were often associated with high Tmax values and absence of infarction. Lacking automatic ways to distinguish artifactual areas, and given that they often are of modest volume, we did not correct for these artifacts; however, future efforts to detect these artifactual regions are needed. Patients who died before the day 90 follow-up imaging represent a possible data bias. Another potential bias is tissue shrinkage by day 90, causing underestimates of the volume of infarction and thereby underestimation of risk for a given Tmax value. Future studies may be able to address this with earlier imaging follow-up, limiting the influence of atrophy.

The probabilistic approach to infarct prediction used in this study is not novel and positron emission tomography studies have demonstrated a probabilistic, rather than threshold-based, relationship between acute perfusion and

Figure 3. A, Infarct risks by treatment arm (tissue-type plasminogen activator=29; placebo=33). B, Infarct risks by recanalization status (recanalization=18; no recanalization=11). Bars indicate maximum and minimum values, boxes indicate interquartile ranges, and lines and numbers in the boxes indicate median values.
Several methods have been proposed that integrate information from several modalities and use a variety of transformation techniques to estimate the infarct probability. However, these techniques still have not found widespread use despite their theoretical appeal. The method presented here only uses DWI and PWI to classify a mismatch and is simple to implement. It does require exclusion of false-positive areas, in our case performed by a manual exclusion of false-positives, which is relatively quick to perform (3–5 minutes). The actual calculation of the predicted volume is then a few algebraic operations of microseconds in duration. To the best of our knowledge, a severity-weighted mismatch definition has not been presented before. In addition, a map of infarct risk can be generated by substituting each Tmax strata with the associated probability to produce a visual topographical representation of infarct risk in the individual. In its current form, the method does not require coregistration to calculate a volumetric mismatch; however, as fully automated registration is becoming increasingly available, it is likely that registering the acute DWI to the PWI could provide more accurate mismatch estimates that account for DWI regions already reperfused. With coregistered data, it would also be possible to attribute higher infarct risks to tissue already DWI-positive, irrespective of the concurrent Tmax value.

There are some limitations to this study. First, the analyzed cohort was small and we had a limited number of patients without recanalization. The estimated probability of infarction in each Tmax strata could be improved by a larger cohort with acute PWI and follow-up images, and it would enhance the predicted infarct volume by the severity-weighted approach. Second, regarding all perfusion parameters, Tmax is sensitive to several hemodynamic effects and this is bound to introduce some variability in the risk estimates. Third, our estimates of risk will be affected by fluctuating perfusion levels. Ideally, this analysis could be improved by limiting it to nonreperfusing tissue as determined by coregistration of acute and follow-up perfusion imaging. Unfortunately, they day 3 reperfusion assessment in these data makes this impossible for patients with edema, which peaks at day 3 to 5 and is largest in patients without reperfusion, which is exactly the group of interest. Earlier reperfusion assessments, at the end of infarct evolution, but before severe edema development, may partially address this issue. Limiting the at-risk region to nonreperfused tissue, albeit limited by coregistration errors, did not significantly improve prediction of final infarct volume over those based on Tmax ≥8-second estimates. Fourth, the mismatch calculation in this study assumes that DWI is a reasonable representation of a core matter that remains controversial, but this topic previously has been systematically examined.

Figure 4. Infarct risks in each Tmax strata for the 11 patients with no recanalization. The plot highlights intrapatient variability. The infarct risk generally is increasing with Tmax in the individual, although often with a plateau beginning at approximately the 12 to 14 strata. The plot also highlights interpatient variability. The severity–risk relationship in the individual is subject to considerable variability across patients. It is clear from this plot that a threshold approach may not be the best way to model the continuous relationship between Tmax and risk of infarction.
in this data set and has been found to have negligible impact on mismatch classifications.\textsuperscript{24}

Despite these limitations, this study demonstrated that the probability of infarction is strongly tied to the severity of PWI deficits. A penumbral definition based on $T_{\text{max}} \geq 2$ is now considered inadequate because of a penumbral definition and our results corroborating this (showing that $T_{\text{max}}$ 2 seconds to $T_{\text{max}}$ 4 seconds have a median risk of only 8%); also, in the absence of more severe areas of hypoperfusion, a penumbral definition of 2 seconds would grossly overestimate the area of final infarction.\textsuperscript{25}

In summary, we have shown that infarct risks increased with the severity of perfusion deficits and that in a small population of 11 patients a probabilistic method for infarct volume prediction outperforms all $T_{\text{max}}$ thresholds statistically, with exception of the $T_{\text{max}} \geq 10$ threshold, for which it was only favored by a trend. Thus, although we do not provide formal evidence that the proposed method performs better than using a $T_{\text{max}} \geq 10$ threshold, the data suggest it is of potential interest and deserves further investigation in larger samples. It would seem ideal to perform both the reperfusion and final infarct assessments at an earlier time point to minimize the confounding effects of late futile reperfusion and infarct shrinkage.

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Disclosures
None.

References
8. Calamante F, Christensen S, Desmond PM, Ostergaard L, Davis SM, Connelly A. The physiological significance of the time-to-maximum (Tmax) parameter in perfusion MRI. *Stroke*. 2010;41:1169–1174.
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Abstract

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Yoshinari Nagakane, MD, PhD1; Soren Christensen, PhD2; Toshiyasu Ogata, MD, PhD3; Leonid Churilov, PhD3;4; Henry Ma, MBBS1; Mark W. Parsons, PhD5; Patricia M. Desmond, MD, FRACP4; Christopher R. Levi, FRACP6; Kenneth S. Butcher, MD, PhD5; Stephen M. Davis, MD, FRACP2; Geoffrey A. Donnan, MD, FRACP1; for the EPITHET Investigators

1 National Stroke Research Institute, Florey Neuroscience Institutes, Austin Health, University of Melbourne, Australia; 2 Department of Neurology, Royal Melbourne Hospital, University of Melbourne, Australia; 3 Department of Mathematics and Statistics, University of Melbourne, Australia; 4 Department of Neurology, Hunter Medical Research Institute, John Hunter Hospital, University of Newcastle, Australia; 5 Department of Neurology, University of Alberta, Edmonton, Alberta, Canada; 6 Department of Radiology, Royal Melbourne Hospital, University of Melbourne, Australia.

Abstract

Background and Objectives: The mismatch volume defined by perfusion-weighted images that exceed diffusion-weighted images is used as a marker of ischemic penumbra tissue. Threshold setting for perfusion lesion determination is expected to be a useful tool. In multiple studies using contrast-enhanced computed tomography, a probabilistic relationship between perfusion and infarction has been demonstrated. In this study, we used data from a randomized comparative trial of acute ischemic stroke with tissue plasminogen activator (EPITHET) to (1) quantify the relationship between low perfusion severity (Tmax by measurement) and infarction risk, (2) use this relationship to define a two-division mismatch based on infarction risk, and (3) evaluate the response to treatment in patients with a mismatch identified by this new definition.

Methods: Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) patients were included. Baseline perfusion-weighted images and T2-weighted images at 90 days were superimposed. The perfusion lesion volume was divided into 10 layers based on the Tmax delay, and the risk of infarction was defined by a specific Tmax layer at 90 days.

Results: The risk of infarction was an increasing function in all subgroups, including the cohort. In contrast, the probability approach was more useful than a threshold approach of Tmax for all Tmax thresholds, except for Tmax ≥ 10.

Conclusions: The risk of infarction and treatment effectiveness increased with increasing perfusion abnormality. This indicates that a new definition of the mismatch, which focuses on severity, can more accurately define penumbra tissue.