Use of MRI to Estimate the Therapeutic Window in Acute Stroke

Is Perfusion-Weighted Imaging/Diffusion-Weighted Imaging Mismatch an EPITHET for Salvageable Ischemic Brain Tissue?

Gabor Toth, MD; Gregory W. Albers, MD

The fundamental goal of many acute stroke therapies is rapid arterial recanalization leading to reperfusion of critically hypoperfused brain tissue. Clinical benefits of this therapeutic approach require the presence of a salvageable penumbra. It is estimated that salvageable tissue is present in up to 80% of patients with stroke who present rapidly, but these capricious zones of potentially recoverable parenchyma typically disappear within the first 6 to 12 hours after symptom onset.1 The rate of disappearance of the penumbral tissue appears to vary considerably between individuals based on a variety of physiological factors, predominantly the availability of adequate collateral circulation. How to quickly and reliably identify these fortunate patients who may have a prolonged therapeutic window has been the ultimate quest of a large volume of modern cerebrovascular neuroimaging research.

A leading approach to this challenge has been to estimate the ischemic penumbra based on the difference between the volume of tissue that exhibits a disturbance in cerebral blood flow, as assessed by perfusion-weighted MRI (PWI), and the volume of tissue that has already developed evidence of advanced ischemic injury reflected by cytotoxic edema on diffusion-weighted MRI (DWI).2 The “mismatch” regions (areas of PWI abnormality that do not have corresponding DWI lesions) have been considered likely to benefit from reperfusion therapies. This hypothesis has been assessed in a variety of recent clinical trials, including DIAS, DEDAS, DIAS II, DEFUSE, and now, most recently, EPITHET.3–7

EPITHET was a randomized, double-blind, placebo-controlled trial designed to determine whether intravenous tissue plasminogen activator, administered 3 to 6 hours after stroke onset, would reduce infarct growth in patients with PWI/DWI mismatch.2 Because technology to rapidly and accurately determine which patients have a PWI/DWI mismatch was not available, both mismatch and nonmismatch patients were enrolled, but the primary analyses were performed on patients who were subsequently determined to have at least a 20% “mismatch” based on blinded assessment of the baseline PWI and DWI images. PWI images were postprocessed using an arterial input function to adjust for variability in the arrival of the intravenous contrast bolus between patients, and the results were expressed as a Tmax (time when the residue function reaches maximum) map using a threshold of 2 seconds.

EPITHET enrolled 101 patients with moderate–severe stroke (median National Institutes of Health Stroke Scale score 13) who were treated at a median time of slightly less than 5 hours from symptom onset. A high proportion of these patients (86%) were considered to have a mismatch based on postprocessing of the PWI and DWI images. The primary efficacy end point was reduction in the geometric mean relative growth between the baseline DWI lesion and a 90-day T2-weighted image among mismatch patients. Approximately a 30% reduction lesion growth was noted in the tissue plasminogen activator-treated patients; however, this difference was not statistically significant. Many of the secondary analyses (growth >0%, median relative growth) did yield statistically robust results, especially when patients with DWI lesions of less than 5 mL were excluded.

PWI-documented reperfusion (defined as a ≥90% reduction between baseline and Day 3 PWI volumes) occurred in 56% of the tissue plasminogen activator-treated patients compared with 26% of the placebo group (P=0.01). When patients who experienced reperfusion were compared with those who did not reperfuse, there was a compelling difference in all measures of infarct growth (P≤0.001). Furthermore, favorable clinical outcomes were also more common in mismatch patients with reperfusion; 63% of the patients who reperfused achieved a 90-day modified Rankin Scale score of 0 to 2 versus 32% who did not reperfuse (P=0.007). These

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From the Stanford Stroke Center, Department of Neurology and Neurological Sciences, Stanford University Medical Center, Palo Alto, Calif. Correspondence to Gregory W. Albers, MD, Stanford Stroke Center, 701 Welch Road, Suite 325, Palo Alto, CA 94305. E-mail albers@stanford.edu

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results confirmed the results of the nonrandomized DEFUSE trial that documented a significantly higher rate of favorable clinical outcomes in mismatch patients who achieved early reperfusion compared with mismatch patients who did not reperfuse.6

In EPITHET, mismatch patients treated with tissue plasminogen activator had a nonsignificant trend toward good neurological outcome compared with the placebo patients (50% versus 37%). The authors estimated that a sample size of approximately 225 patients per group would likely be adequate to demonstrate differences in their primary outcome between tissue plasminogen activator- and placebo-treated patients.

Although the results of EPITHET provide support for the potential of MRI-based patient selection, we believe they also indicate that additional work is required to refine these techniques before initiating more definitive clinical trials.

How Should Mismatch Be Defined?
Techniques for defining mismatch have varied between studies. Interestingly, 86% of patients were found to have mismatch in EPITHET, which is greater than the percentage of patients with acute stroke who are estimated to have significant volumes of salvageable tissue based on positron emission tomography studies8,9 and is also greater than documented in some similar MRI trials. For example, the recent DEFUSE study had similar entry criteria, yet found only 54% of the patients to have a “mismatch.”10 Whether this difference is related to differences in the patient populations enrolled versus differences in PWI analysis techniques is yet to be determined. DEFUSE patients had slightly lower median National Institutes of Health Stroke Scale scores at baseline (11.5 versus 13) and baseline DWI volumes that were on average approximately 10 mL smaller than the EPITHET patients (21 versus 10 mL), yet the median baseline PWI volumes in EPITHET were more than 100 mL larger than in DEFUSE. This raises the possibility that the PWI analysis techniques used in EPITHET led to identification of larger volumes of tissues as abnormal on PWI.

One of the concerns raised about bolus contrast PWI techniques is the potential to overestimate critically hypoperfused tissue.10 In addition to identifying tissue truly at high risk of permanent ischemic injury, PWI may identify areas of benign oligemia that will survive regardless of whether an effective intervention occurs.11,12

Bolus contrast PWI techniques identify perfusion abnormalities in the brain by assessing the timing of the arrival of an intravenous contrast bolus. The PWI lesion volumes obtained can differ significantly based on the specific PWI parameters chosen for analysis such as Tmax, time-to-peak, mean transit time, cerebral blood volume, or cerebral blood flow.13,14 The PWI volumes will also vary depending on whether they are “corrected” based on an evaluation of an arterial input function.15,16 The PWI maps that are quickly processed by the software that accompanies most modern MRI scanners are not corrected for arterial input. Furthermore, the lesion volumes will also vary considerably based on the specific threshold chosen to represent a PWI lesion. For example, the volume of tissue with a Tmax delay of 2 seconds is typically considerably larger than the volume with a delay of 4 or 6 seconds. A major challenge is to determine the optimal thresholds, PWI processing methods, and analysis techniques that most accurately estimate the volume of critically hypoperfused tissue in patients with acute stroke.

Scrutiny of the data from the DEFUSE study demonstrates that PWI techniques that correct for the arterial input function appear to provide better prediction of clinical outcomes than noncorrected techniques.17 In addition, the use of higher Tmax thresholds (>4 to 6 seconds versus >2 seconds) improves the accuracy of predicting final infarct volumes and penumbral salvage18 and correlates better with critical hypoperfusion on Xenon CT.19 Supportive data are also available from patients with acute stroke studied back-to-back with PWI and positron emission tomography; a Tmax threshold of 5.5 seconds was found to be the optimal Tmax cut point for identification of the penumbral threshold as determined by positron emission tomography.20

To date, most clinical trials have not chosen to use arterial input function corrected or thresholded PWI maps because until recently, user-friendly software has not been available to process these maps in real time. Failure to postprocess PWI maps may have contributed to suboptimal agreement between local investigators and central reading committees regarding which patients actually have a mismatch. For example, in the DEDAS trial,4 32% of the patients enrolled were determined by the central imaging laboratory to have violated the MRI inclusion criteria; in half of these violations, the local investigators interpreted the MRI as demonstrating a mismatch that was not confirmed by the core laboratory. Overestimation of the true volume of critically hypoperfused tissue may have contributed to the failure of the recently reported DIAS 2 trial to document benefits of the thrombolytic desmoteplase in “mismatch patients.” When the DIAS 2 data were analyzed with a more conservative definition of mismatch (PWI-DWI volume >75 mL), beneficial effects of the thrombolytic agent desmoteplase were more apparent.5

We consider EPITHET to be a landmark trial because it helps confirm the feasibility and promise of using PWI/DWI selection for future trials of acute stroke therapies. It also highlights some of the current limitation of MRI selection; optimal PWI processing algorithms require clarification and validation, and rapid automated methods that can identify relevant DWI and PWI lesions need to be refined and incorporated into modern MR scanners. International efforts to achieve these objectives are currently underway. If adequately acquired and processed, the PWI/DWI mismatch may become a sensible epithet for salvageable tissue.

Disclosures
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References


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