Beyond Mismatch
Evolving Paradigms in Imaging the Ischemic Penumbra With Multimodal Magnetic Resonance Imaging

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**Background**—The ability to quickly and efficiently identify the ischemic penumbra in the acute stroke clinical setting is an important goal for stroke researchers and clinicians. Early and accurate identification of potentially salvageable versus irreversibly infarcted brain tissue may enable selection of the most appropriate candidates for early stroke therapies and identify patients who may still benefit from late recanalization or neuroprotective treatment. Recent advances in magnetic resonance imaging of the ischemic penumbra have been driven by serial MRI studies characterizing the natural evolution of cerebral infarction as well as the brain’s response to reperfusion.

**Summary of Comment**—Based on these studies, various models for imaging the penumbra with MRI have been proposed, including the pioneering diffusion-perfusion mismatch model and later multivariate approaches. Each model has its own unique advantages and disadvantages.

**Conclusions**—There now are sufficient data to support paradigm shifts in a variety of central tenets regarding MRI and the ischemic penumbra. These include the insights that diffusion-perfusion mismatch does not optimally define the penumbra; that early diffusion lesions are in part reversible and often include both irreversibly infarcted tissue and penumbra; that the visible zone of perfusion abnormality overestimates the penumbra by including regions of benign oligemia; that MRI is a very practical method for acute stroke imaging; and that therapeutic salvage of the ischemic penumbra has been demonstrated in humans using diffusion-perfusion MRI. (*Stroke*. 2003;34:2729-2735.)

**Key Words:** ischemia • magnetic resonance imaging, diffusion-weighted • magnetic resonance imaging, perfusion-weighted • penumbra

“We predict that the impact of [advanced echoplanar MR techniques in acute stroke]…may come to be viewed as analogous to the introduction of electrocardiography for the diagnosis of myocardial infarction, i.e., a rapid, reliable, objective, accurate, and essential emergency diagnostic test that will guide the development and application of acute therapeutic intervention.”

—Warach, Annals of Neurology, 1995

The promise of acute stroke therapies is anchored in the assumption that an ischemic penumbra exists in humans for several hours or more after symptom onset and that this tissue may be salvaged with restoration of blood flow or effective neuroprotective treatments. While recent trials have demonstrated that thrombolytic therapies are successful in the early time windows,1 there remains a crucial need to identify patients with existing salvageable tissue over longer time periods since these patients may benefit from late recanalization therapies.

There are a variety of definitions of the ischemic penumbra.2–5 For the purposes of this discussion, the penumbra will be defined as tissue that is at risk of infarction but still salvageable and that is the target of acute stroke therapy. Penumbral tissue needs to be distinguished from the ischemic core (tissue that is already irreversibly injured even if blood flow is reestablished) and from tissue experiencing benign oligemia, in which the mild reductions in tissue perfusion do not actually place the tissue at risk.

Stroke is a heterogeneous disorder, and the duration of the penumbra in humans varies substantially from person to person depending on a variety of factors, including location of the vessel occlusion, degree of collateral blood flow supply, intrinsic susceptibility to ischemia of tissues hypoperfused (eg, gray versus white matter), and other patient-specific factors. Direct visualization of the location and extent of the penumbra could greatly improve our ability to determine which patients may benefit from therapy and allow treatment decisions to be based on individualized pathophysiology rather than arbitrary chronological time windows.

In the past decade, diffusion- and perfusion-weighted MRI techniques have revolutionized the role of MRI in the...
evaluation of patients with acute cerebrovascular disease.\textsuperscript{6} Diffusion-weighted imaging provides a measure of tissue bioenergetic compromise and perfusion-weighted imaging a measure of hemodynamic compromise. The combined data from these 2 modalities can delineate the pathophysiological state of ischemia and may provide a practical means to rapidly and precisely identify the ischemic penumbra in the acute stroke setting. This article will address the successes and failures of initial MRI models of the ischemic penumbra as well as the unique opportunities and challenges to expanding the clinical applications of multimodal MRI of the penumbra in the acute stroke setting.

**MRI Models of the Ischemic Penumbra: Diffusion-Perfusion Mismatch**

One of the most exciting concepts that arose from early reports employing diffusion-perfusion MRI in acute stroke was that diffusion-perfusion mismatch provided a simple and feasible means to identify the ischemic penumbra. According to this model (Figure 1), the diffusion abnormality represents core, irreversibly injured tissue, and the outer rim of the visualized perfusion abnormality defines the periphery of the penumbra. The region with perfusion abnormality but no diffusion lesion (the mismatch region) identifies tissue that is hypoperfused but that has not yet experienced advanced bioenergetic failure and represents the penumbra.\textsuperscript{7}

The most compelling data supporting the mismatch model come from observations that the natural history of early diffusion abnormalities in untreated patients is to grow over time into the area of the initial perfusion abnormality as the penumbra gradually fails.\textsuperscript{8} An analysis of data from placebo-treated patients enrolled in 2 neuroprotective studies demonstrated that lesions grew on average by 144\% to 180\% from the baseline to the follow-up imaging studies.\textsuperscript{9,10}

In contrast, several analyses of patients experiencing reperfusion (either spontaneously or therapeutically with thrombolytics) have shown inhibition of diffusion lesion growth, suggesting actual salvage of the mismatch region (Figure 2). For example, Jansen and colleagues\textsuperscript{11} demonstrated inhibition of lesion growth in patients experiencing reperfusion compared with patients with persistent perfusion deficits or vessel occlusions. More recently, Parsons and colleagues\textsuperscript{12} compared MRI signatures in patients treated with intravenous tissue plasminogen activator within 6 hours of onset compared with a group of matched controls. They found a significant decrease in the amount of mismatch tissue that proceeded to infarction in the thrombolysis-treated group. Of note, substantial regions of diffusion-perfusion mismatch have been clearly visualized in acute posterior as well as anterior circulation ischemia, with salvage of mismatch regions also demonstrated after thrombolytic therapy.\textsuperscript{13}

A second important observation has been that significant diffusion-perfusion mismatch may be present up to 24 hours or more from symptom onset. Darby and colleagues\textsuperscript{14} demonstrated that while the presence and volume of mismatch progressively decreases over time, approximately 60\% to 70\% of patients up to 24 hours will still have substantial

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**Figure 1.** Schematic of the mismatch model for defining the ischemic penumbra. DWI indicates diffusion-weighted imaging.

**Figure 2.** Example of therapeutic salvage of mismatch region when early reperfusion is established with thrombolytic therapy. This patient presented with left hemiparesis and sensory loss and at angiography was found to have a right internal carotid artery occlusion. The initial pretreatment MRI (top) shows marked mismatch with only small, scattered diffusion-weighted imaging (DWI) lesions despite a hemispheric perfusion deficit on the T\textsubscript{max} perfusion map (time to peak of the residue function). The posttreatment MRI after vessel recanalization with intra-arterial thrombolysis shows that the perfusion deficit has resolved completely without significant change in the initial DWI lesions. PWI indicates perfusion-weighted imaging.

**Figure 3.** Percentage of patients with mismatch over time. Adapted from Darby et al.\textsuperscript{14}
regions of mismatch (Figure 3). This finding is supported by studies previously performed in stroke patients employing positron emission tomography demonstrating penumbral tissue present in up to 16 to 48 hours after symptom onset. These findings suggest that the time window available for salvage of the penumbra in select patients may be much longer than the traditional, presumed 3- to 6-hour window and that diffusion-perfusion MRI has the ability to identify these patients.

Challenges to the Mismatch Model

Despite these initial successes, recent studies have demonstrated that the simple diffusion-perfusion mismatch model is only a rough approximation of the ischemic penumbra. The standard mismatch model is based on 2 assumptions: (1) the border of visualizable perfusion-weighted imaging abnormality demarcates penumbral tissue from tissue not at risk, and (2) the border of the diffusion-weighted imaging abnormality demarcates core, irreversibly infarcted tissue from penumbral tissue (Figure 4). It is now known that both of these claims are flawed.

Challenge 1 to the Mismatch Model: Penumbra Versus Benign Oligemia

The first major challenge to the mismatch model is differentiation of true penumbra from tissue experiencing benign oligemia. Initial studies performed in the 1970s by Astrup and colleagues identified 3 types of tissue with abnormal blood flow: (1) irreversibly damaged tissue (cerebral blood flow <6 to 10 mL/100 g per minute); (2) ischemic penumbral tissue: functionally silent tissue that could be salvaged if blood flow was restored (cerebral blood flow 10 to 20 mL/100 g per minute); and (3) oligemic tissue (cerebral blood flow below normal range but not at risk of infarction).

When the standard mismatch model was first promulgated, it was not widely appreciated that the border between abnormal- and normal-appearing tissue evident to the human interpreter on most perfusion maps includes some regions of benign oligemia. Careful subsequent studies have demonstrated that although the natural history of the diffusion abnormality is to grow into the mismatch zone, this growth generally encompasses a substantial proportion, but not all, of the region of visible perfusion abnormality.

How to best demarcate the outer limits of the perfusion abnormality to include only penumbra and not benign oligemia has been the focus of recent intensive research efforts. Several groups have attempted to address this issue by studying the evolution of diffusion and perfusion lesions in untreated patients. These natural history studies have the potential to differentiate penumbra from benign oligemia by assessing tissue fate in the worst-case scenario (recanalization does not occur). Tissue with an initial perfusion abnormality but no diffusion abnormality that proceeds to infarction is considered to have been within the penumbral region, while tissue with an initial perfusion abnormality that does not proceed to infarction is considered to have been within the benign oligemic region. A range of apparent diffusion coefficient (ADC) and perfusion thresholds have been identified that differentiate between penumbra and benign oligemia with modest degrees of accuracy.

However, several factors constrain the predictive value of the isolated ADC or perfusion thresholds determined in these studies. One limitation is that some patients likely experience spontaneous recanalization, even without interventional therapy, at undetermined time intervals after baseline imaging, contaminating the putative nonreperfusion population. Moreover, variations in methodology between centers limit the widespread utility of these findings. Furthermore, it is unlikely that isolated ADC or MR perfusion measures acquired at a single time point will be sufficient to make these differentiations because of interindividual variations in timing of scan acquisition, blood pressure, collateral flow, and other metabolic conditions.

For these reasons, several groups have been developing multivariate models that incorporate information obtained from multiple MRI sequences to predict tissue outcome in untreated patients. Various models have been developed employing logistic regression analysis, generalized linear algorithms, multiparametric ISODATA techniques, and other automated strategies. All of these approaches have demonstrated good overall accuracy; however, they are limited in their generalizability since they have been based largely on patients imaged relatively late after onset. Additional studies with larger sample sizes and more uniform analytical methodologies are needed to confirm and extend these findings.

Challenge 2 to the Mismatch Model: Core Versus Penumbra

The second challenge to the mismatch model involves differentiation of the true penumbra from the ischemic core, ie, tissue that has already been irreversibly injured even if blood flow is reestablished. The mismatch model assumes that the initial diffusion lesion represents irreversibly infarcted core tissue. However, animal models have demonstrated that diffusion lesions may be partially or even fully reversible when reperfusion occurs within 2 to 3 hours.

Several groups have now replicated these findings in humans, demonstrating that the volume of tissue displaying diffusion abnormality may actually decrease (and in some cases diffusion lesions may be completely reversed) if blood...
Flow is restored at an early time point (Figure 5). MR studies in patients treated with intra-arterial thrombolysis have shown that, early after stroke onset, a very substantial volume of tissue showing diffusion abnormality is actually penumbra rather than core. In the University of California at Los Angeles (UCLA) series of patients undergoing vessel recanalization with intra-arterial thrombolitics, partial or complete reversal of initial diffusion abnormalities occurred in 44% of patients, with an average decrease in size of the initial diffusion-weighted imaging lesion volume of 52%. Although some of the tissue that shows therapeutically driven early reversal of diffusion lesions and abnormal ADC eventually redevelops diffusion abnormalities (late secondary injury), a substantial proportion of tissue, one third in the UCLA series, had evidence of sustained reversal of diffusion abnormalities and ultimate salvage at late imaging.

On the basis of these findings, we have suggested a modified view of the ischemic penumbra as defined by MRI in which the penumbra includes not only diffusion-perfusion mismatch but also portions of the initial diffusion abnormality itself (Figure 6). An important implication of this modified view is that even select patients without diffusion-perfusion mismatch may still derive benefit from thrombolytic therapy.

The fact that diffusion abnormalities can be reversed and fully salvaged in some patients suggests that alternative approaches beyond the mismatch model may be able to more accurately distinguish core from penumbral tissue. Specifically, it is important to study patients undergoing vessel recanalization to develop models that can predict what will happen in the best-case scenario of early and sustained reperfusion. Our group has used an image coregistration technique to study the pretreatment MRI characteristics of tissue that either proceeded to infarction, developed hemorrhagic transformation, or was salvaged in patients who underwent recanalization therapies.

The fundamental paradigm for these studies is to obtain baseline multimodal MRI, perform an intervention that restores perfusion rapidly, and then obtain final outcome imaging. Only tissues that were already irreversibly infarcted before therapy will end as infarct regions, and mapping (coregistration) of final infarct lesions onto pretreatment scans will permit voxel-by-voxel analysis and identification of MR variables that distinguish core from penumbra (Figure 7). Intra-arterial thrombolysis is a particularly powerful technique for this type of study because not only does it permit rapid recanalization, but the final procedure angiogram affords full knowledge of the success and timing of recanalization in individual patients, allowing unambiguous identification of a population of patients experiencing early reperfusion.

Figure 8 shows summary ADC histograms for tissue regions that evolved toward the 3 unique tissue fates (hemorrhagic transformation, infarction, or salvage). The histograms show that tissues that underwent hemorrhagic transformation had lower ADC values than tissues that became infarcted and that the salvaged (penumbral) tissue had the

Figure 5. Example of reversal of diffusion-weighted imaging (DWI) abnormalities after vessel recanalization with intra-arterial thrombolysis.

Figure 6. Modified view of MRI-defined ischemic penumbra in which the penumbra equals not only regions of diffusion-perfusion mismatch but also a portion of the diffusion abnormality itself.

Figure 7. Schematic illustration of the coregistration approach, allowing voxel-by-voxel analysis of pretreatment variables that predict ultimate tissue fate. PWI indicates perfusion-weighted imaging; DWI, diffusion-weighted imaging.
highest (most normal) ADC values. However, substantial overlap between the ADC ranges occurred within the 3 groups, indicating that the ADC value alone cannot fully predict tissue fate. This is further illustrated by calculations of the likelihood of infarction based on individual ADC thresholds. For example, this analysis suggests that a tissue region with ADC <550 μm²/s has a 50% likelihood of infarction even if reperfusion occurs. Use of newer ADC imaging techniques, such as fluid-attenuated inversion recovery (FLAIR) ADC imaging, may improve overall prediction ability of isolated ADC thresholds alone even further.

Multivariate models to predict irreversible infarction despite vessel recanalization, as well as risk of hemorrhagic transformation, have the potential to substantially improve predictive accuracy. In our series, models derived by logistic regression achieved overall accuracy rates of 80% to 81%. The most important predictive variables that entered into both these models were the ADC value (a measure of the intensity and the cumulative extent of ischemic tissue injury experienced up until the time of imaging) and the T_max value (a time-to-peak measure of the severity of tissue hypoperfusion). By comparison, the mismatch model achieved an accuracy rate of only 53%. While this type of multivariate model has the potential to improve overall accuracy in identifying the ischemic penumbra, including some patients without mismatch who might benefit from therapy, it is important to recognize that diffusion-perfusion mismatch often provides a good, rapidly available estimation of the penumbra and a practical means for selecting candidates for therapy.

MRI as a Practical Stroke Tool

While the practicality of MRI as a neuroimaging method for hyperacute stroke has been questioned in the past, there is a growing body of data demonstrating both the feasibility and practicality of this approach. Current stroke MRI protocols take only 5 to 20 minutes to perform and are part of the routine hyperacute stroke workup in many academic stroke centers. Modern high-speed computers can quantitatively predict the outcome of specific regions of brain tissue on the basis of statistical models developed from longitudinal studies in the best-case scenario of complete sustained reperfusion as well as in the worst-case scenario of no reperfusion. This type of postprocessing analysis can be performed within 5 to 15 minutes. Moreover, a growing number of community hospitals have 24-hour MRI capability. Finally, emerging data suggest that MRI may be able to accurately detect hyperacute intraparenchymal hemorrhage, obviating the need for CT studies and suggesting that MRI may be a suitable sole imaging modality for acute stroke.

Future Directions

There are a number of important future directions for MR imaging of the penumbra. Further work is needed to validate quantitative perfusion imaging and demonstrate its ability to differentiate penumbra from benign oligemia. Of particular importance is the need for employment of standardized methodologies for postprocessing and analysis to allow comparison of data across studies and institutions.

Of note, any model developed in patients treated with thrombolytic therapy (either intra-arterial or intravenous) is constrained by a delay of 1 to 2 hours or more from the time of initial imaging to vessel recanalization. Moreover, some thrombolytic agents themselves, including tissue plasminogen activator, may have a toxic effect on cerebral tissue. The most accurate models with the greatest discriminatory power will likely be developed in patients undergoing endovascular procedures (eg, clot retrievers, lasers), which permit ultra-rapid recanalization. These procedures could theoretically be performed in the MRI suite with the appropriate catheters and devices, further minimizing delays.

In addition, rapidly advancing technology will allow validation and incorporation of new MR techniques, including MR spectroscopy, flow heterogeneity measures, and MRI oxygen extraction fraction techniques into acute stroke protocols. These techniques have the potential to further augment existing multivariate models in delineating infarct core, penumbra, and benign oligemia.

Perhaps the most exciting potential application of MRI is its use as a selection tool for acute stroke treatments. The initial excitement surrounding the successful National Institute of Neurological Disorders and Stroke trials showing a benefit of intravenous tissue plasminogen activator when delivered within 3 hours of symptom onset has been tempered by 2 emerging facts: (1) few patients are currently being treated within the 3-hour window, and (2) identification of effective therapies beyond 3 hours from symptom onset remains elusive. While there is clearly a need to extend the time window for treatment, it is important to recognize that the number of patients who will benefit from treatment (those with an existing penumbra) progressively decreases over time. Therefore, a trial of an acute stroke therapy delivered later than 3 hours after onset has the greatest likelihood of showing efficacy if the trial incorporates a method to select appropriate patients for therapy, ie, those with existing salvageable penumbral tissue and decreased likelihood of developing complications from treatment. Multimodal MRI allows therapeutic decisions to be based on individual patient pathophysiological information, allowing the time window to be extended in appropriate patients. However, clinical studies of MRI-guided stroke therapies to date have largely consisted of small case series. To definitively prove the clinical
Applications of MRI in Acute Stroke Clinical Trials

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*Auxiliary/surrogate analyses also planned; Artist-MRI indicates AMPA Receptor Antagonist Treatment in Ischemic Stroke; MR IMAGES, Magnetic Resonance Intravenous Magnesium Efficacy in Stroke; CLEAR, Combination Approach to Lysis Using Eptifibatide and RT-PA; ROSIE, ResPro Retavase Reperfusion of Stroke Safety Study–Imaging Evaluation; DEFUSE, DWI Evolution For Understanding Stroke Etiology; EPITHET, Echoplanar Imaging Thrombolysis Evaluation Trial; MR RESCUE, MR and Recanalization of Stroke Clots Using Embolectomy; DIAS/DEDAS, Desmoteplase in Acute Stroke/Dose Escalation of Desmoteplase; SELECT MR, Stroke Evaluation for Late Endovascular Cerebral Thrombolysis with MR.

utility of this technique, large-scale multicenter clinical trials must be performed to demonstrate not only decreased lesion volumes but also improved clinical outcome in MR-selected patients.

Currently, trials are under way that employ MRI for 3 separate purposes within clinical trial methodology (Table). The first involves studies that use MRI as an auxiliary or surrogate outcome measure, as was pioneered in neuroprotective treatment trials and now continues to be applied in both neuroprotective and reperfusion trials. The second type of trial is designed to confirm the clinical utility of the MRI mismatch hypothesis, as is being done in the DWI Evolution for Understanding Stroke Etiology (DEFUSE) and Echoplanar Imaging Thrombolysis Evaluation (EPITHET) trials. In these trials, all patients in a late time window are treated, irrespective of their pretreatment MR pattern, to test the hypothesis that patients with MRI penumbral patterns will respond to therapy while those with MRI nonpenumbral patterns will not. The third type of trial actually employs MRI to select for treatment only patients with appropriate MRI patterns. The Desmoteplase in Acute Stroke/Dose Escalation of Desmoteplase (DIAS/DEDAS) studies enroll patients with mismatch patterns, and the Stroke Evaluation for Late Endovascular Cerebral Thrombolysis With MR (SELECT MR) trial enrolls patients with penumbral patterns and low risk of hemorrhagic transformation on the basis of MR predictive models. These latter studies are designed to extend the time window for late treatments by selecting only patients with favorable MRI patterns.

Conclusions

There are sufficient data to support paradigm shifts to a variety of novel concepts regarding MRI and the ischemic penumbra. These include the insights that diffusion-perfusion mismatch does not optimally define the penumbra; that early diffusion lesions are in part reversible and often include both irreversibly infarcted tissue and penumbra; that the visible zone of perfusion abnormality overestimates the penumbra by including regions of benign oligemia; that MRI is a very practical method for acute stroke imaging; and that therapeutic salvage of the ischemic penumbra has been demonstrated in humans with the use of diffusion-perfusion MRI. The future is promising; it is only a matter of time before MRI assists us in individualizing therapeutic decisions and identifying effective therapies for acute ischemic stroke that can be delivered at late time points.

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