Evolving Paradigms in Neuroimaging of the Ischemic Penumbra

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Abstract—Identification of the ischemic penumbra in the acute stroke clinical setting is an important goal for stroke researchers and clinicians. Various models for imaging the penumbra with MRI have been proposed, including the pioneering diffusion–perfusion mismatch model and later multivariate approaches. A number of multicenter clinical trials are now under way to test these models and confirm the utility of MRI-based treatment decisions. Present knowledge about MRI visualization of the salvageable penumbra suggests a promising future in which MRI studies are performed routinely in the acute stroke setting and the data provided by these MRI studies assist in individualizing therapeutic decisions and identifying effective therapies that can be delivered at late time points. (Stroke. 2004;35[suppl I]:2662-2665.)

Key Words: acute care ■ magnetic resonance imaging ■ stroke, acute

The promise of acute stroke therapies is based on the premise 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. Although recent trials have demonstrated thrombolytic therapies are successful in the early time windows,1 there remains a crucial need to identify the subgroup of patients with existing salvageable tissue over longer time periods because these patients may benefit from late recanalization therapies.

Although there are a variety of definitions of the ischemic penumbra, perhaps the most clinically relevant definition of the penumbra is tissue that is at risk but still salvageable and that is the target of acute stroke therapy.2–5 Multimodal MRI currently provides a number of approaches to identifying the penumbra in the acute stroke setting in real time. However, a challenge for stroke neuroimaging is not only to identify the penumbra but also to differentiate this region 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.

The introduction of diffusion-weighted and perfusion-weighted MRI into the clinical stroke arena in the 1990s transformed the field of acute stroke neuroimaging. Diffusion-weighted imaging provides a measure of tissue bioenergetic compromise and perfusion-weighted imaging a measure of hemodynamic compromise. One of the most promising concepts that arose from early reports of diffusion–perfusion imaging was the notion that diffusion–perfusion mismatch could identify the ischemic penumbra. According to this model, the diffusion abnormality represents core irreversibly injured tissue (Figure 1). This theory developed in part 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.6 For example, 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.7,8 In contrast, several analyses of patients experiencing reperfusion (either spontaneously or therapeutically with thrombolytics) have shown inhibition of diffusion lesion growth, suggesting that actual salvage of the mismatch region has occurred.9,10

A second important observation has been that significant mismatch may be present up to 24 hours or more from symptom onset. Darby et al demonstrated that although the number of patients with mismatch progressively decreases over time, 44% of patients imaged between 18 to 24 hours still had mismatch,11 providing supportive evidence that the time window available for salvage of the penumbra in select patients may be much longer than the traditional 3- to 6-hour window.

However, several fundamental challenges to the mismatch model have been raised. The first challenge is differentiation of true penumbra from tissue experiencing...
benign oligemia. This becomes an important focus for perfusion MRI because a number of studies have demonstrated that the perfusion-weighted imaging abnormality often overestimates the final infarct volume. Thus, with the mismatch model, the region of mismatch may overestimate the amount of tissue that is truly at risk. A second major challenge to the mismatch model is the assumption that the initial diffusion lesion represents irreversibly infarcted tissue. Various studies have demonstrated that in humans, as in animal stroke models, diffusion lesions may be reversed if blood flow is restored at an early time point (Figure 2). Based on these findings, a modified model of the penumbra has been proposed in which the penumbra includes the diffusion–perfusion mismatch region (minus the region of benign oligemia) as well as a portion of the initial diffusion abnormality itself (Figure 3). An important implication of this modified view is that select patients without diffusion–perfusion mismatch may still derive benefit from recanalization therapy.

To address these challenges to the mismatch model, a number of groups have attempted to identify perfusion or apparent diffusion coefficient thresholds that may better differentiate the regions. The results of these studies have revealed 2 important findings. First, there is a pressing need for standardization of methodological approaches to image postprocessing and analysis to allow pooling of data and cross-comparison of results across studies. Second, absolute or relative thresholds alone are not highly accurate in predicting tissue fate.

The fact that diffusion abnormalities can be reversed and fully salvaged in some patients combined with the finding that single parameter thresholds are not highly accurate suggests that alternative approaches to the mismatch model may be able to more accurately distinguish core from penumbral tissue as well as distinguish penumbral tissue from benign oligemia. Various models have been developed using logistic regression analysis, generalized linear algorithms, multiparametric ISODATA techniques, and other automated strategies. All of these approaches have demonstrated good overall accuracy; however, additional studies with larger sample sizes and more uniform analytic methodologies are needed. In the future, emerging new techniques such as magnetic resonance spectroscopy and calculation of oxygen extraction fraction and cerebral metabolic rate of oxygen utilization using MRI may be incorporated into these predictive models to improve accuracy of these types of models.

Perhaps the most promising progress in the field is a growing body of clinical data suggesting the usefulness of using MRI to select patients for late reperfusion therapies. Parsons et al reported the results of a retrospective analysis of patients with diffusion–perfusion mismatch treated with intravenous tissue plasminogen activator between 3 and 6 hours from symptom onset compared with historical controls. The tissue plasminogen activator-treated mismatch patients had substantially greater recanalization, smaller infarct volume, greater penumbral salvage, and greater

![Figure 1](http://stroke.ahajournals.org/)

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

![Figure 2](http://stroke.ahajournals.org/)

**Figure 2.** Example of therapeutic salvage of the mismatch region and reversal of diffusion lesion after vessel recanalization with intra-arterial thrombolytic therapy. The initial pretreatment MRI (top row) shows marked diffusion–perfusion mismatch in a patient with a right middle cerebral artery occlusion (perfusion-weighted imaging image is Tmax perfusion map – time to peak of the residue function). The post-treatment MRI after vessel recanalization with intra-arterial thrombolysis shows that both the perfusion and perfusion deficits have resolved.

![Figure 3](http://stroke.ahajournals.org/)

**Figure 3.** 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.
Applications of MRI in Acute Stroke Clinical Trials

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*Auxiliary/surrogate analyses also planned.


Clinical improvement. The Desmoteplase in Acute Stroke investigators reported the results of a dose escalation trial of the novel thrombolytic desmoteplase.28 Patients were treated 3 to 9 hours from symptom onset. Diffusion–perfusion mismatch was required for study enrollment. The investigators found a dose-related response on clinical outcome and in early reperfusion rates.

Kidwell et al performed an analysis of a subset of patients treated with mechanical embolectomy up to 8 hours from symptom onset and studied pretreatment and post-treatment with MRI.29 Approximately half of the patients had a penumbral pattern pretreatment and recanalization was achieved in 70% of patients. At day 90, 89% of patients with a penumbral pattern and recanalization had a good neurologic outcome (modified Rankin score 0 to 2) compared with only 14% of patients without a penumbral pattern but with recanalization. These data suggest only patients with an MRI-defined penumbral pattern are likely to benefit from therapy.

These studies lay the groundwork for the large-scale, multicenter, randomized, controlled, clinical trials that are necessary to definitively prove the theory that multimodal MRI can be used to improve selection criteria for acute treatment based on individual patient pathophysiology. A number of clinical trials are now underway to demonstrate not only decreased lesion volumes but also improved clinical outcome in MR-selected patients (Table).

In summary, the data available to date support a number of conclusions. The perfusion deficit includes regions of benign oligemia and therefore overestimates the penumbra. Mismatch may provide a simple and practical approximation of the penumbra; however, some diffusion lesions are reversible; therefore, the penumbra may include not only the mismatch region but also a portion of the diffusion-weighted imaging lesion. Although absolute diffusion and perfusion thresholds are only of modest usefulness in differentiating core, penumbra, and benign oligemia, multivariate predictive models and newer techniques (oxygen extraction fraction, magnetic resonance spectroscopy) may improve accuracy of these predictive models. Although salvage of the MRI-defined penumbra has been demonstrated in humans, ongoing clinical trials are designed to demonstrate the usefulness of MRI selection of patients for late recanalization therapies.

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