Mismatch and Defuse
Harvesting the Riches of Multicenter Neuroimaging-Based Stroke Studies

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The goal of acute stroke evaluation is to determine not only stroke type (ischemic versus hemorrhagic) and localization (anatomical and vascular), but perhaps more importantly, to determine reversibility (presence of an ischemic penumbra that may be salvaged with acute therapy). Traditionally, neurologists have relied on history and neurological examination to provide much of this information. However, long experience has demonstrated that the neurological examination is imperfect at best in determining lesion localization and grossly limited in its ability to provide insights into the presence of penumbral tissue. This is evidenced by the only modest correlations between National Institutes of Health Stroke Scale (NIHSS) score and perfusion-weighted imaging lesion volume.1,2

The last decade has seen a striking growth in neuroimaging techniques that provide important real-time information about acute stroke pathophysiology. In the mid-1990s the advent of diffusion-weighted imaging revolutionized the role of MRI in acute stroke evaluation. Not only could diffusion-weighted imaging provide evidence of tissue injury within minutes of symptom onset, but also the diffusion-perfusion mismatch model offered a simple and practical means of identifying the ischemic penumbra and thus patients most likely to respond to reperfusion therapies, particularly in the late time window (>3 hours from symptom onset).3 Multiple prior studies have shown that if blood flow is not restored, the diffusion lesion will grow into the mismatch region and become a permanent infarct.4 Although this model continues to offer an imperfect approach to defining the penumbra, it has clearly been shown to provide a good approximation of penumbral tissue.5–7

Davalos and colleagues first proposed the clinical-diffusion model (CDM) as an alternative means to estimate the presence of penumbral tissue.8 According to this model, NIHSS score substitutes for perfusion-weighted imaging lesion volume.8 According to this model, NIHSS score substitutes for perfusion-weighted imaging lesion volume because it was felt that perfusion imaging was technically challenging and that many centers with diffusion-weighted imaging capability did not have perfusion-weighted imaging capability. In their study of 166 patients with a hemispheric ischemic stroke of <12 hours duration, CDM was defined as a diffusion-weighted imaging lesion volume <25 mL and an NIHSS score ≥8. They found that patients with CDM were more likely to have infarct growth and early neurological deterioration compared with those without CDM.

In this month’s issue of Stroke, Lansberg and colleagues report the results of an analysis of clinical-diffusion and perfusion-diffusion mismatch models to predict the presence of penumbra from patients enrolled in the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) trial.9,10 This report provides not only new important data addressing this specific question, but also reminds us of several additional important insights into acute stroke evaluation and neuroimaging.

First, the authors demonstrate in a large, well-designed, prospective treatment study of IV tissue plasminogen activator administered 3 to 6 hours from symptom onset, the limited role of the clinical-diffusion mismatch model for identifying salvageable brain tissue in the acute stroke setting. There was no agreement beyond chance between the 2 mismatch models. Moreover, patients with diffusion-perfusion mismatch model were more likely to achieve good clinical outcome with reperfusion compared with those without; however, this association was not true for patients with CDM. These findings are not unexpected. Our routine clinical experience has shown us that a small, strategically located lesion can mimic involvement of a much larger vascular territory and, alternatively, a large lesion of a relatively silent region can evade detection on the NIHSS score. It is also important to note that perfusion-weighted imaging is no longer technically challenging—most current scanners capable of diffusion imaging are fully equipped for performing perfusion imaging as well as postprocessing.

This is an important reminder that every step away from pathophysiology introduces error and will be a less accurate predictor of tissue outcome and physiological response to intervention. Second, we are reminded that the neurological examination, and by default the NIHSS, are imperfect instruments to describe ischemic pathology (by size, region). A third important insight from this study is that, to date, there is no perfusion postprocessing algorithm or mismatch definition that is clearly superior to others. This finding points to the need for standardization and comparisons on large pooled data sets.

In summary, the authors are to be congratulated not only for demonstrating the usefulness of perfusion-diffusion mismatch compared with clinical-diffusion mismatch in acute stroke therapy, but also providing us with a glimpse of the wealth of data and knowledge that will be forthcoming from
large, well-designed, multicenter clinical trials and collaborations of neuroimaging-based acute stroke therapies.

**Disclosures**

None.

**References**


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