Understand the role of imaging in stroke has quietly moved forward on several fronts in 2005, without any very major breakthroughs. We will highlight articles that illustrate aspects of the continuing debate about the utility of MR and computed tomography (CT) in selecting patients for therapy, assessing outcomes, determining stroke etiology and risk of new events.

We begin our sampling of 2005 highlights with an angiographic study that relates to the physiological premise of brain perfusion studies. We should not be surprised to be reminded that there is a close relationship between the neurological severity of the stroke as measured on the National Institutes of Health Stroke Scale (NIHSS) score and the site of cerebral arterial occlusion—a proximal internal carotid artery occlusion is likely to cause a more severe stroke than a distal middle cerebral artery (MCA) branch occlusion—but Fischer and colleagues have taken that one step further by actually placing predictive values for the presence and site of a cerebral arterial occlusion on the NIHSS score.1

For example, among 226 patients undergoing intra-arterial angiography within 4 to 6 hours of acute ischemic stroke, an NIHSS of ≥10 was associated with an internal carotid artery occlusion in 97% and a vertebrobasilar artery occlusion in 96%; an NIHSS of ≥12 was associated with an intracranial arterial occlusion in 91% of cases.

There has been uncertainty over the role of early signs of ischemia on noncontrast CT in patient assessment for thrombolysis. Systems for scoring the extent of early signs of ischemia, like the Alberta Stroke Program Early CT Score (ASPECTS), focus the eye on the MCA territory and probably help by making sure the observer systematically examines each bit of the MCA territory. Demchuk and colleagues applied ASPECTS to the National Institute of Neurological Disorders and Stroke (NINDS) tissue plasminogen activator (tPA) trial CT scans.2 Among these CT scans from 624 patients within 3 hours of acute stroke collected between about 1990 and early 1995, 57% had early infarct signs when looked at systematically with ASPECTS, but there was no evidence of a treatment modifying effect of early signs of ischemia on thrombolysis. In other words, patients with early signs of ischemia had similar outcomes to those without early signs of ischemia after thrombolysis.

Further study of the mismatch between clinical deficits and early CT changes in acute stroke has been proposed as a method of identifying patients who have hypoperfused but still have viable brain. Using the ASPECTS score to estimate cerebral injury among a sample of patients and their CT scans from 4 IV thrombolysis trials, Kent and colleagues found that the “Clinical-CT mismatch” did not identify patients more or less likely to respond to tPA therapy.3 Thus, although early signs of ischemia on CT are diagnostically meaningful, as of now they do not inform the decision about whom to treat with tPA. The use of the ASPECTS has also been applied to CT perfusion parameter maps to predict tissue fate with and without reperfusion.4 In patients with major reperfusion, mean cerebral blood volume and time-to-peak signal intensity ASPECTS closely predicted final infarct ASPECTS. In patients without major reperfusion, mean cerebral blood flow and mean transit time ASPECTS best predicted final infarct ASPECTS. Further work is needed to establish the predictive value of these parameters in the hyperacute phase (ie, before it is known whether the patient is going to reperfuse).

Across a selection of centers that routinely use advanced MRI, there is no consensus about MRI selection criteria to be used for tPA therapy.5 Local practices range from the routine use of MRI as the sole imaging screen before <3-hour tPA to restricting use of MRI beyond 3 hours and treating in that time period only patients with a diffusion-perfusion (DWI/PWI) mismatch who do not qualify for clinical trials. Otherwise, the use of the MRI DWI/PWI mismatch for thrombolytic selection is largely confined to clinical trials. Studies continue to accumulate evidence that the specific algorithm for calculation of mismatch is less important than the presence or absence of mismatch. The Desmoteplase in Acute Stroke Trial (DIAS) included patients with an MR PWI/DWI mismatch of >20%, defined by each investigator’s preferred technique, later confirmed by a single method in the core laboratory as 95% accurate.6 The most striking imaging finding in DIAS was that improved clinical improvement at 90 days after desmoteplase versus placebo was tracked in a dose dependent manner to patients with evidence on mean transit time of early reperfusion. A more detailed analysis comparing quantitative mismatch definitions was reported by Butcher and colleagues from the ongoing Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET) of tPA 3 to 6 hours from onset.7 Tissue reperfusion was more predictive of outcome than the mismatch, regardless of how mismatch was defined or measured.
The debate over the best definition of mismatch should not obscure the validity and utility of this application of the "ischemic penumbra" concept, which is a mainstay of preclinical and clinical testing of acute stroke therapies. Recent positron emission tomography studies confirm the relationship of the DWI lesion and the DWI/PWI mismatch to metabolic and hemodynamic changes, but also confirm the heterogeneity of cerebral metabolic rate for oxygen and oxygen extraction fraction within those regions.\(^8,9\) The variation in DWI lesions and difficulties in precisely relating early DWI changes to tissue state and perfusion values in stroke patients should not be surprising because 2 commonly-used strains of laboratory rat can show very different patterns of evolution in apparent diffusion coefficient and the DWI hyperintensity when subjected to the same middle cerebral occlusion insult (patients must be substantially more variable).\(^10\)

The debate about what causes cerebral small vessel disease (including subcortical infarction) continues. DWI is important to reliably identify not just the index symptomatic subcortical lesion, but also other silent contemporaneous or sequential subcortical ischemic events. Several articles have reported identification of other subcortical DWI hyperintense lesions (ie, in addition to the symptomatic lesions) of similar age on DWI at presentation,\(^11\) suggesting either recurrent emboli or some other ongoing active process. Multiple subcortical lesions on DWI at presentation identified patients who were more likely to have a potential embolic cardiac or large artery source, although the proportion that actually had multiple lesions on DWI was small. Of course, multiple subcortical lesions could arise through other mechanisms, microvascular disease, lipohyalinosis, which may occasionally affect more than one vessel to the point of causing ischemia simultaneously. Perhaps with more widespread use of DWI in large cohort studies with long-term imaging follow-up at regular intervals, it will be possible to observe new silent white matter lesions appearing and study associated risk factors more closely.

Further insights into cerebral small vessel disease are beginning to emerge with imaging. A 3-dimensional (D) volume analysis of MR images of lacunar infarcts in 10 patients with CADASIL showed that although many of the infarcts were spherical or ovoid, about a fifth were oblong, sometimes with an extended "tail."\(^12\) The calculated volumes of many of the lesions were smaller than would be expected for a sphere of diameter 1.5 cm, suggesting that 2-D imaging may give the impression that lacunar infarcts are larger than when assessed in 3-D. Alternatively, many of the infarcts studied would have been asymptomatic: asymptomatic lacunae are typically smaller than symptomatic ones, and the edge detection mechanism used in the image processing may have underestimated the lesion sizes. Nonetheless, sophisticated techniques for visualizing small vessel detail, such as this and tractography, are now emerging, making unraveling the mysteries of subcortical ischemic stroke a serious possibility in the near future. We look forward to substantial developments in this field in the next year.

### References

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