The year in neuroimaging of stroke began with a lively response to a paper published at the end of 2001 by the NINDS rt-PA Stroke Study Group regarding the controversial topic of the clinical significance of early subtle CT signs of ischemia in response to rtPA therapy.1 That paper continued the series of post-hoc analyses coming from the NINDS rt-PA clinical trial data to support the position that all patients selected by the criteria used for enrollment in these trials may benefit from acute rtPA therapy, regardless of specific baseline features. This study by Patel et al1 was featured at the 2002 International Stroke Conference and engendered a passionate discussion both at the conference and in the literature2 on the use of early CT ischemia signs as potentially exclusionary criteria. The study reviewed CT films from the trial, generated from scanners of the early 1990s. After adjustment for group imbalances in several baseline clinical features, most notably clinical severity by NIH Stroke Scale, early ischemic changes were not predictive of symptomatic intracerebral hemorrhage, death at 90 days, or clinical deterioration at 24 hours. A marginal association was observed between overall 90-day outcome and early ischemic changes. When compared with the placebo patients without ischemic changes, only rtPA–treated patients without CT changes had favorable 90-day outcomes; however, within the subgroup of patients with most extensive CT changes, there did remain a treatment effect on the 90-day Rankin score. Modern scanners and analysis of the digital images are likely to be more sensitive and accurate in detecting early ischemic changes and may lead to less ambiguous conclusions. Until then, the question of whether extensive early ischemic changes on CT identify poor responders to standard rtPA therapy remains an open one.

The potential of other CT measures of early ischemia measures, most notably CT perfusion, have been increasingly explored in 2002. The diagnostic value of CT angiography (CTA) source images, which reflect the distribution and concentration of contrast in the regions within a slice, have been suggested as superior to noncontrast CT and comparable to lesion volume measurements on diffusion MRI (DWI),3–5 but a comparison study with PET raised a cautionary note against overestimating the diagnostic accuracy of this approach.6 The CTA source image method gives a qualitative assessment most related to cerebral blood volume, and poor blood volume by any method is a reliable predictor of infarct, thus the method will likely prove to provide valid diagnostic information. More direct measures of cerebral blood flow with contrast CT look promising for measuring acute hemodynamic compromise and predicting infarct risk.5,7–9 Although conceptually appealing as an add-on to routine emergency noncontrast CT, the contrast perfusion CT technology is still limited by restricted slice coverage. As with any technical advance, enthusiasm and advocacy run many years ahead of validation and general application. The studies at present are few, and conclusions are preliminary. Additional technical developments and assessment of the impact of CT contrast perfusion methods on acute stroke therapeutics will need to be assessed in future years.

Monitoring of patients for 2 hours after initiation of thrombolytic therapy with transcranial Doppler ultrasonography, Alexandrov and Grotta10 described reocclusion in 34% of patients with any evidence of early recanalization. This reocclusion was associated with better outcome than patients with stable occlusions but associated with worse outcome than patients with stable recanalization. This study provides a rationale for the development of supplemental therapy to improve recanalization rates over standard rtPA therapy.

The coming of age of MRI diffusion and perfusion methods is evidenced by their use as the gold standard against which the above-referenced CT perfusion studies are compared. A large consecutive series of >500 acute stroke admissions evaluated by CT and DWI and retrospectively analyzed confirmed the sensitivity and specificity of DWI of >90% in the overall sample as well as the <6-hour subgroup, greater than that of CT and conventional MR.11 The first prospective, randomized comparison of CT and DWI <6 hours from onset in 50 patients confirmed the >90% accuracy and superior interrater reliability of DWI.12 The superiority to CT was most pronounced in the less experienced readers (residents), a finding of greatest relevance to the real-world use of emergency neuroimaging of stroke.12

The potential of MRI diffusion and perfusion in selecting patients for thrombolysis beyond 3 hours and evaluating the tissue effects of reperfusion was the subject of 3 preliminary yet influential studies. An open-label pilot study reported by Parsons et al13 suggested that patient selection by diffusion and perfusion MRI and MRI evaluation of response to treatment may identify the patients in whom intravenous rtPA therapy will be of clinical benefit when therapy is initiated between 3 and 6 hours. The subgroup of 16 patients with perfusion-diffusion mismatch in that study had a statistically significant degree of recanalization, reperfusion, and tissue salvage relative to untreated historical controls. It is provoc-
Example of late secondary injury demonstrated in a 27-year-old female who presented with left hemiparesis and hemisensory loss. This patient was treated with combined intravenous/intraarterial rt-PA for branch right MCA occlusions. The pretreatment MRI study shown on the top row shows substantial DWI and ADC abnormalities in the right MCA territory with an associated perfusion deficit visualized in blue on the relative cerebral blood flow (rCBF) map. The middle row (postthrombolysis) shows corresponding images obtained 3 hours after vessel recanalization, demonstrating marked decrease in the volume and intensity of the DWI and ADC lesions and the early appearance of relative hyperperfusion appearing in red and yellow. The bottom row shows partial reappearance of the lesions at day 7, associated with a more pronounced region of hyperperfusion. Courtesy of C. Kidwell, UCLA Stroke Center.

ative that the 16 mismatch patients treated with rtPA also showed a statistically significant clinical response relative to 16 matched controls. This sample is an order of magnitude fewer patients than required to show clinical benefits in the rtPA trials, which did not select patients on the basis of imaging pathology. Similar observations were reported in a larger series, also open-label, with contemporaneous but not randomized comparison of 76 treated to 63 untreated patients. Inevitably, randomized placebo-controlled trials will have smaller effects than open-label pilot studies, and such studies are underway to test whether the patient with the DWI-PWI mismatch will clinically benefit from intravenous rtPA between 3 and 6 hours.

After reperfusion, apparent recovery of ischemic tissue—normalization of diffusion and perfusion abnormalities without development of a lesion on T2WI—followed by a subsequent deterioration of the tissue has been described in animal models. Kidwell et al reported a similar phenomenon in some patients undergoing intraarterial thrombolysis (Figure). Their results from 18 patients undergoing intraarterial therapy found that reversal of DWI abnormality on reperfusion in 8 patients was followed by a secondary decline in apparent diffusion coefficient (ADC) and infarct development in 5 of those 8. A trend toward lower NIH Stroke Scale scores and lower ADC values was also suggested in patients with the secondary decline, and the authors hypothesize that this imaging phenomenon may represent a therapeutic target for postreperfusion neuroprotective therapies.

Predicting the fate of tissue and clinical outcome from early MRI diffusion and perfusion measurement remains a topic of great interest and little consensus. Hyperacute (<6 hours) DWI lesion volume of >89 mL may be predictive of early neurological deterioration. Flow heterogeneity maps from perfusion MR may be more accurate predictors of final infarct than mean transit time maps. A combination of relative peak height and time to peak perfusion MR measurements may be a better predictor of infarct growth than quantitative hemodynamic parameters. Multiparametric imaging, such as the most recent ISODATA approach, which combines diffusion, perfusion, and T1-weighted and T2-weighted imaging, may be best of all in predicting tissue fate and clinical outcome. There may be inaccuracies of present measurements of the ADC because of contamination from cerebrospinal fluid (CSF). The study by Latour and Warach demonstrated that conventional DWI and ADC measurements are significantly contaminated by CSF contained within some of the measured voxels. By combining DWI with fluid-attenuated inversion recovery in a single sequence, CSF signal was suppressed in 31 patients with ischemic lesions of <6-hour duration. The ADC was measured in ~28 000 ischemic and 28 000 normal voxels. Without CSF suppression, mean ADC and its SD in ischemic brain were ~40% higher than when measured with CSF suppression (0.85 [0.26] to 0.60 [0.18]×10⁻³ mm²/s⁻¹). The difference was even greater for normal tissue. Approximately 25% of ischemic pixels had healthy ADC values because of CSF contamination. The effect of CSF suppression on ADC measurement may affect the accuracy predictive models that use ADC thresholds, and the ultimate predictive model will need to account for this effect.

References


