Advances in Stroke 2004

Imaging

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Acute Stroke

The Melbourne group reported further application of the positron-emission tomography (PET) hypoxia marker 18F-labeled fluoromisonidazole (F-MISO).1-3 In one article, they further developed and validated their novel imaging methodology to map the penumbra using this tracer.1 Applying this method, they elegantly showed that hypoxia affects white matter to a similar degree and extent as gray matter, suggesting the former has at least as high a resistance to ischemia than the latter and that its salvage should help to maximize benefit of treatment.2 In a third article,3 they report that the apparent diffusion coefficient decreases can be found in either DWI/PWI lesion may still represent, at least in part, salvageable penumbral tissue, and that, consistent with earlier evidence, appropriate interventions should improve outcome even beyond 24 hours.

The year 2004 has seen the first, long-awaited, articles reporting direct PET and diffusion-weighted imaging (DWI)/perfusion-weighted imaging (PWI) comparisons.4-6 Using state-of-the-art diffusion tensor imaging (DTI) and fully quantitative PET as gold standard, Guadagno et al4 documented that the acute DWI lesion not only contains irreversibly damaged, but also penumbral tissue, in agreement with studies showing potential reversibility of the DWI lesion, while even severe apparent diffusion coefficient decreases can be found in either tissue category. One therapeutic implication is that a matched DWI/PWI lesion may still represent, at least in part, salvageable tissue. Comparing the predictive value of DWI and 11C-Flumazenil (FMZ) for final infarction, Heiss et al6 found that although both have similar overall predictive power (around 84% of the final infarct), false-positives occurred with DWI but not with FMZ, consistent with the Guadagno et al findings.4 Assessing the validity of PWI to assess the at-risk tissue by means of PET, Sobesky et al6 concluded that overall the simple DWI/PWI mismatch overestimates the penumbra, but the use of time-to-peak (TTP) delay maps helps toward solving this problem, with TTP delays >4 s being best suited. These results apply specifically to the TTP method of deriving magnetic resonance imaging (MRI) perfusion maps; other methods, such as mean transit time (MTT) maps, may be less prone to overestimate the region of symptomatic ischemia.7 Thijs et al8 found large variations in hypoperfusion lesion size with different arterial input function (AIF) locations used to derive MRI perfusion maps. They found that the AIF derived from the contralateral middle cerebral artery (MCA) gave ischemic volumes that most accurately predicted follow-up lesion volume.

The sensitivity of MRI relative to computed tomography (CT) has now been established for acute hemorrhage diagnosis in patients with focal stroke symptoms of less than 6 hours duration. Susceptibility-weighted MRI, most commonly the gradient-recalled echo (GRE) sequence, is used for that purpose. Fiebach et al9 found near perfect discrimination of hemorrhagic from ischemic stroke on MRI in a sample containing 62 cases of each, obtained in <6 hours: 100% sensitivity among experts; 95% sensitivity among medical students after a brief tutorial. Kidwell et al10 prospectively investigated a broad sample of 200 stroke patients, in which MRI followed by CT was obtained in <6 hours. The consensus of 4 experts’ independent, blinded reads found MRI superior for detecting any hemorrhage (because of MRI sensitivity to micro- and other chronic bleeds) and equivalent for acute hemorrhage, which was diagnosed by both modalities in 25 patients. There were 8 discrepant reads, 4 in either direction, for acute hemorrhage. Three of the discrepant cases of acute hemorrhage on CT were also diagnosed by MRI but classified incorrectly as chronic hemorrhage. However, 4 cases of acute hemorrhagic transformation on MRI were missed on CT. Smaller retrospective series have also reported cases of hemorrhagic transformation evident on susceptibility-weighted MRI but not CT following thrombolytic therapy,11,12 including cases where CT findings were equivocal because of residual angiography contrast.11

As evidence continues to confirm that prethrombolysis severity of clinical or MRI parameters predict outcome with recanalization, so does evidence that resolution of perfusion deficits is predictive of clinical recovery. Singer et al13 reported that greater amounts of at-risk tissue did not progress to infarct among patients who had recanalized relative to those who had not in a sample of 17; 80% of the MTT defect and 78% of the TTP ≥2 s delayed region did not progress to infarct on follow-up imaging. Chalela et al14 reported in a sample of 42 patients that resolution of at least 30% of the volume of MTT defect by 2 hours after standard IV tissue plasminogen activator treatment was associated with excel-
lent clinical outcome (modified Rankin score of 0 or 1). This degree of early reperfusion was a stronger predictor of outcome than pretreatment clinical severity or the volume of pretreatment diffusion or hypoperfusion lesion. This 30% early reperfusion criterion associated with 90-day clinical recovery in thrombolytic therapy was confirmed in the Desmoteplase In Acute Stroke (DIAS) Trial, a randomized placebo controlled trial that found a similar dose positive response on both early reperfusion (using 30% or greater resolution of MTT volume) and excellent 90-day clinical outcome. Significant clinical benefits at the highest dose were observed when this thrombolytic therapy was initiated 3 to 9 hours from onset. The DIAS trial also illustrated that the simple diffusion-perfusion mismatch, although an overestimate of true penumbra, may effectively select the target population for intravenous thrombolytic trials beyond the 3-hour time window.

There is growing interest in understanding the potential role of tissue inflammation after stroke. Using single photon emission computed tomography (SPECT) and \(^{11}\text{In}\)-tropanolate-labeled neutrophils, Price et al longitudinally studied cerebral neutrophil recruitment after MCA stroke. Significant neutrophil recruitment was demonstrated within 24 hours of onset and shown to attenuate over time. Neutrophil accumulation appeared to correlate significantly with infarct expansion. PET studies using the activated microglia-specific ligand \(^{11}\text{C}\)-PK11195 are now awaited.

Three novel applications of MRI contrast material show promise for clinical application. Invasion of macrophages into the evolving infarction has been demonstrated in patients with T1-weighted MRI by Saleh and colleagues following injection of ultrasmall superparamagnetic iron oxide (USPIO) particles, which are taken up by macrophages 1 week after injection of ultrasmall superparamagnetic iron oxide (USPIO) particles, which are taken up by macrophages 1 week after injection. PET studies using the activated microglia-specific ligand \(^{11}\text{C}\)-PK11195 are now awaited.

Latour and colleagues identified gadolinium enhancement on fluid-attenuated inversion recovery MRI of the intrasulcal and other hemispheric CSF spaces indicative of blood brain barrier disruption <12 hours after onset of ischemia in acute stroke patients. This enhancement pattern was associated with reperfusion, risk of hemorrhagic transformation and worse clinical outcome and was exacerbated by treatment with thrombolytics, suggesting this marker may have utility in evaluating strategies to decrease hemorrhagic risk of thrombolytics.

Barber and colleagues demonstrated binding of a novel MRI contrast agent, gadolinium-DTPA-sLe(x) A, to activated endothelium in a mouse ischemic stroke model. Such targeted contrast agents might one day find clinical application in developing therapeutic strategies addressing inflammatory response to ischemia/reperfusion.

**Carotid Disease**

It is well established that in patients with symptomatic internal carotid artery (ICA) occlusion the presence of misery perfusion or severely impaired vasodilatory reserve considerably increases the risk of subsequent ipsilateral stroke, justifying ongoing trials of extracranial/intracranial bypass on selected patients. Yamauchi et al found evidence that by resetting the oxygen needs of the tissue the occurrence of cortical metabolic depression (secondary to diachisis or selective neuronal damage in patients with striatocapsular infarction) might “mask” misery perfusion in ICA disease, a confounder that will be important to consider in future studies. In the same vein, Kuroda et al found that patients with ICA disease and reduced cerebral blood flow but normal vasodilatory reserve had cortical metabolic depression and proportionally reduced cortical FMZ binding, suggesting selective neuronal damage. Thus, cortical metabolic depression may afford protection from further ischemic events distal to ICA disease.

In 2002, \(^{18}\text{F}\)-2-fluorodeoxyglucose–PET was shown to be able to detect inflammation within carotid plaques in vivo. This year, a novel tracer to detect plaque inflammation was reported in a preliminary form. Kietselaer et al used SPECT and \(^{99m}\text{Tc}\)-annexin A5 to label apoptotic cells. They report increased uptake in symptomatic carotid bifurcations subsequently shown to exhibit evidence of plaque instability at histology, whereas stable plaques did not show increased uptake before endarterectomy. This type of approach may allow in the future the detection of patients most at risk of ischemic event—perhaps independently of degree of stenosis. Using USPIO-enhanced MRI with histological correlation, Trivedi et al found areas of signal intensity reduction within the plaque in 7 of 8 symptomatic patients, corresponding to USPIO particles accumulation in macrophages, with imaging being optimal 24 to 36 hours after contrast infusion.

**Plasticity**

A substantial number of functional MRI (fMRI) studies have addressed the neural processes underlying motor recovery after stroke. Although difficult to achieve, several longitudinal studies assessed both clinical recovery and fMRI patterns over time. Expanding on earlier studies, Ward et al showed that as recovery proceeds, there is correlated decrease in the amount of activation in widespread motor areas bilaterally, indicating less neural recruitment needed to perform the same task over time. Across patients, the amount of activation in these areas correlated with the severity of motor deficit at each time point, but a few cortical areas showed a significant change in this relationship, suggesting different rehabilitation strategies might be required as recovery proceeds. Excessive contralesional M1 activation is present during hand movement from the early stages after stroke, but does not appear to contribute directly (ie, via the uncrossed corticospinal tract) to recovery of affected hand as shown by single-pulse transcranial magnetic stimulation applied in the same patients; it might be part of a widespread top-down recruitment in an effort by the stroked brain to perform the task. In parallel with recovery under regular physiotherapy however, the activation pattern tends to return toward a more ipsilesional, ie, physiological, pattern. Consistent with this, intensive gait training is associated with shifts of activation toward the ipsilesional hemisphere, which correlate with the amount of gait...
recovery.\textsuperscript{31} In a randomized controlled trial, Luft et al\textsuperscript{32} found that relative to regular physiotherapy, additional bilateral arm training was associated with increased activation of bilateral motor areas, more so contralaterally, during affected elbow flexion-extension movements. This suggests that contralateral M1 activation may be useful for enhanced motor function after stroke, which may however relate to the proximal limb movement or the bilateral training used, or more likely to the fact that the patients were all severely affected. Studying patients with sensorimotor cortex infarcts during tactile exploration, Binkofski and Seitz\textsuperscript{28} found focal activation in the cortex adjacent to the infarcted area as early as a few days from stroke, consistent with earlier studies indicating that survival of the peri-infarct penumbra offers opportunities for cortical map reorganization.

In addition to fMRI, more studies using DTI in stroke are beginning to appear.\textsuperscript{33,35} Fractional anisotropy mapping was used to assess the presence and severity of corticospinal tract disruption, be it by direct damage\textsuperscript{36} or secondary Wallerian degeneration.\textsuperscript{34} Combining fractional anisotropy mapping or full DTI-derived tractography with fMRI should help to better understand the mechanisms underlying recovery. New methods to map progressive focal or extensive atrophy following stroke\textsuperscript{36} may also find similar applications.

References


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