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The Roles of Diffusion and Perfusion MR Imaging in Acute Stroke Management

The development of new therapies for treating the acute stroke patient has produced demands for sophisticated imaging and physiologic evaluation, as demonstrated in the excellent article by Ueda et al appearing in this issue of the *AJNR* (page 983). Anticoagulant and antiplatelet therapy have been used for years to prevent intraarterial thrombus formation. A thrombolytic agent, tissue plasminogen activator (tPA), was approved for intravenous use by the FDA in June 1996. The favorable results of the multicenter, prospective, and double-blind study revealing the efficacy of intraarterial Pro-urokinase (Pro-UK), when administered within six hours of the onset of acute ischemia, have been announced (1). Numerous articles reference the intraarterial use of urokinase and tPA (2–4). Many mechanical devices have been recommended for opening the occluded vessel. Although many neuroprotective agents have been evaluated, to date none have been found to be efficacious.

The pretreatment exclusion of hemorrhage by imaging is essential if anticoagulation, antiplatelet therapy, or thrombolysis is to be used. Nonetheless, the morbidity from the use of new thrombolytic agents requires far more from imaging, such as the use of perfusion and diffusion MR imaging techniques that are described in the article by Ueda et al.

Intravenously administered tPA produces intracranial hemorrhage in 6% to 20% of cases, depending upon the time of treatment after onset of the ictus (5, 6). Pro-UK also produces bleeding in a significant percentage of cases, although not always productive of increased symptoms. Given the morbidity and mortality of these risky therapies, it is essential to maximize the risk-benefit ratio. The potential for salvaging the ischemic brain must be defined. The reversibility of the ischemic process not only depends on the time after ictus, but is primarily a function of the degree of persistent collateral flow to the affected tissues. Brain tissue without sufficient collateral flow will die within minutes, whereas tissue with good collateral flow will remain viable. In the latter circumstance the ischemic process potentially can reverse for hours, beyond the limits of 3 to 6 hours that have been established for thrombolytic agents (7). A myriad of image-based techniques are currently available to evaluate cerebral blood flow (CBF), or ''perfusion,'' and the status of the cerebral parenchyma. A brief review of these methods will help put the MR techniques and results described by Ueda et al in perspective.

Plain CT is widely available and rapid, but relatively insensitive to the subtleties of differentiating reversible from irreversible ischemia. Xenon-enhanced CT provides a rapid, quantitative determination of CBF. Identification of the extent of infarction can be made based on the measurement of CBF flow (mL/g of tissue/minute) within combined white and gray matter. A measurement of 10 mL/100 g of tissue/minute indicates infarction has occurred within minutes, a value of 10–22 mL/100 g/minute suggests potentially reversible neurologic dysfunction, and a flow of 22–40 mL/100 g/minute reveals the presence of oligemic tissue (8). Perfusion CT is a qualitative evaluation of the intracranial transit time of a bolus of contrast agent after intravenous injection (9). Single-photon emission CT (SPECT) after the intravenous injection of a radionuclide, such as radioactive technetium attached to the carrier hexamethylpropyleneamineoxime (Tc-99m-HMPAO), is also a qualitative technique for evaluating ''perfusion.'' This technique, with the use of tPA, recently has been shown by Ueda et al to be capable of differentiating those patients who are at risk for hemorrhage from those who have potentially reversible ischemia, regardless of the time elapsed after stroke onset (7). Perfusion MR is currently qualitative, but provides information regarding numerous perfusion parameters, such as cerebral

blood volume (CBV), mean transit time (MTT), and CBF (10, 11). Diffusion MR depicts the effects of altered perfusion on the cerebral parenchyma. Ischemia primarily produces changes in membranes and proteins and secondarily effects shifts in the diffusion of water (12, 13).

Hence, some of these methods (xenon-CT, perfusion CT, perfusion MR, and SPECT) define cerebral perfusion either quantitatively or qualitatively. Some of them (plain CT, diffusion MR) show the effects of ischemia on tissue. Which one or combination of these methods will be best for determining how much tissue is ischemic but viable, justifying the potential morbidity of intervention?

Because altered perfusion is a problem with ischemic stroke, it would seem logical to use a perfusion method. Other than xenon-CT, however, the perfusion methods described are qualitative, or ''semiquantitative'' at best (ratios of values in regions of interest). MR imaging is a powerful technique, providing unsurpassed contrast resolution and the ability to rapidly determine MTT, CBV, time-to-peak change in signal intensity, and CBF flow after a single intravenous injection of contrast material. Unfortunately, all of these calculations provide relative, not absolute, values. The ability to differentiate reversible from irreversible ischemia with perfusion MR imaging alone has not been established. Although the threshold for producing an abnormality on the diffusion MR image is probably between 35 and 40 mL/100 g tissue/minute (13), it has been speculated by some that, in the clinical setting, abnormality revealed by diffusion MR imaging represents irreversible ischemia (14). Hence, the perfusion abnormality outside the inner core of the diffusion abnormality (the ''mismatch'') represents both the reversibly ischemic and dysfunctional tissue (the ''penumbra'') and the larger area of functional but oligemic tissue (10). The determination of the relative size of these components may help to determine the relative risk-benefit ratio of therapy and the clinical outcome.

How good are these assumptions? Is a diffusion abnormality representative of irreversible ischemia? Or, because the perfusion threshold for such an abnormality is above the level of infarction, is it not quite possible that a tissue might be oligemic only, in part or in total, and that increased perfusion, caused either spontaneously or by treatment, may reverse the process at least in part? Because perfusion MR imaging reveals many degrees of perfusion abnormality in a qualitative manner, does it lead to significant overestimation of the eventual infarction? How accurate are diffusion and perfusion MR imaging for predicting the size of the infarct in a patient not treated with thrombolysis? Such accuracy may impact the decision to undertake thrombolysis in another patient.

The study by Ueda et al is significant in that these investigators used a battery of MR perfusion and diffusion maps, and followed the patients for a mean of 8.3 months to assess the value of these methods at predicting outcome. None of the patients received thrombolytic or neuroprotective drugs to confound the prediction of infarction and the measurement of its size. Isotropic maps of the apparent diffusion coefficients (ADCs) were used rather than diffusion-weighted imaging in order to avoid false-positive interpretations caused by gradient directionality and T2 ''shine-through.'' Unfortunately, their patient population did not include the patients of greatest interest: those with ischemia of less than a 6-hour duration. Rather, they studied patients whose ischemic episode had started 6 to 72 hours before imaging.

The ADC, rMTT, and rCBV maps were statistically equal in their sensitivity for the presence of ischemia of any degree. The rCBV, not the ADC, map was the most specific for the presence of infarction. In fact, 25% of this small series of ADC maps were ''false positive'' for ischemia that did not go on to infarction. Lastly, the ADC maps led to overestimated measurement of the size of the eventual infarctions. These data suggest that diffusion MR does, indeed, depict the reversibly ischemic tissue in addition to the irreversible. Additionally, these patients were not treated with thrombolytic drugs; there may have been even more reversibly ischemic tissue that could have been salvaged with the use of aggressive therapy.

The size of the eventual infarction was best predicted by the use of the rCBV map. It is not surprising that the rMTT maps overestimated the size of the eventual infarctions, because this method depicts altered hemodynamics in tissue that may receive sufficient collateral flow from more circuitous routes. The ADC map also led to overestimated measurements of infarction size, which is contrary to other reports (10, 12, 15). Nonetheless, overestimation should not be a total surprise. Given the complexities of primary vascular supply and collateral flow, the ischemic region is probably composed of varying levels of oligemia, without the well-defined boundaries so often depicted. Some of these tissues will recover, and some will evolve to infarction. In addition, the authors correctly point out the increased time between stroke onset and scanning in their patient population (mean, 58 hours) relative to other studies in which scanning was performed within 12 hours. Vasogenic edema may have complicated the interpretation of the diffusion data in the Ueda study. These investigators are currently evaluating the use of quantitative ADC values that may make diffusion data more predictive of the status of the tissue.

Ueda and colleagues help us understand the complexities and the evolution of the ischemic process, which is vital if we are to make rational decisions regarding treatment. In the future, these and other investigators need to perform similar batteries of MR sequences in larger patient populations. It would be preferable to study patients within the first 6 hours after ictus, those most likely to have tissues that can be salvaged with aggressive thrombolytic techniques, among others. I believe that

quantification of both diffusion and perfusion parameters will be essential for differentiating the reversible from the irreversibly ischemic tissue. Comparisons will have to be made between the MR techniques and xenon-CT, perfusion CT, and SPECT CBF analyses to determine the most cost-effective and efficacious methods for defining the salvageable brain. I am convinced that the risk-benefit ratio of aggressive therapy can be determined with such imaging techniques. Lastly, I believe that thrombolysis and other forms of image-guided therapy will be performed by MR or CT scanning and a battery of scans will be obtained before therapy to evaluate salvageable tissue, and after treatment to detect potential complications and determine early therapeutic efficacy.

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Intralesional Injection of Absolute Alcohol into Vertebral Hemangiomas: A New Treatment Option?

Hemangiomas of the vertebral bodies are commonly encountered, being found in 10–12% of patients in autopsy series (1). The vast majority of these are solitary, are discovered incidentally, and are seldom symptomatic. Symptoms, when they do occur, can vary from chronic, poorly defined pain to cord compression and paraplegia. These undesirable consequences are usually caused by compression fracturing, hematoma, epidural extension of a hemangioma, or bony expansion of the vertebral body (1, 2).

A variety of treatment options exists for addressing symptomatic hemangiomas. Surgery is well established, and has been proved effective. A surgical approach is technically challenging because of the markedly vascular nature of these congenital vascular malformations. The introduction of presurgical embolization has facilitated surgery significantly, and is now commonly performed (2). Scattered reports of treatment of symptomatic lesions with embolization alone exist; however, treating these lesions exclusively with embolization is generally inadequate in the majority of cases. Radiotherapy also has been used in treatment of these lesions, usually as a complement to surgery. Radiation therapy alone is often inadequate.

In 1994, Heiss et al reported two patients with spinal cord compression who improved appreciably after direct percutaneous injection of alcohol into vertebral body hemangiomas (3), and then they reported on seven patients 2 years later (4). In this issue of the *AJNR*, Goyal et al (page 1091) report their experience with 14 patients they treated with this technique, considerably expanding the reported number of patients in the literature. The authors found that 86% of their patients demonstrated appreciable clinical improvement in a manner analogous to those reported by Heiss et al.

Direct alcohol injection has several advantages. It is readily performed using conventional bone biopsy equipment and CT guidance without requiring the facilities of an operating room or the sophisticated equipment needed in an interventional angiography suite or radiotherapy unit. Only intrave-