Apparently, Diffusion Coefficient Value and Stroke Treatment Remains Mysterious

Diffusion-weighted imaging (DWI) has become a well-recognized tool in the diagnostic armamentarium of neuroradiologists. The ability of DWI to depict acutely ischemic tissue in the appropriate clinical setting with high sensitivity and high specificity has made DWI the diagnostic method of choice whenever the question of brain ischemia is raised. We know that the high signal intensity on a DWI of an infarct is due to the restriction of water mobility in a voxel of tissue; this appearance represents tissue that keeps much of its baseline signal intensity while all the normal tissue loses its signal intensity as the diffusion-encoding gradients are applied. In short, the apparent diffusion coefficient (ADC), the number that describes water mobility, decreases in ischemic tissue compared with normal values; this change indicates decreased microscopic dephasing in ischemic tissue.

Despite the widespread acceptance of this technique, many fundamental questions about DWI remain. Chief among these is, "Why does ADC decrease?" The short answer is this: We do not know for sure. Fortunately, a tremendous amount of work has been done in animal models to investigate the answer to this question (recently and masterfully reviewed in reference 1), and, therefore, we do know some things. Current evidence indicates, for example, that the ADC decrease is associated with energy failure and cytotoxic edema or the swelling of the cells related to a depolarization-induced water influx from the extracellular compartment. Why this water influx causes a decrease in the ADC value is still unclear, because current data suggest that the water mobility decreases with acute ischemia both inside and outside the cell.

A lack of precise understanding about the biophysical mechanisms by which the ADC decrease occurs does not preclude us from using DWI as a diagnostic tool in the clinic, but an air of mystery around the meaning of DWI does persist. After all, in experimental models, a number of nonischemic events (eg, administration of an excitotoxin such as *N*-methyl-D-aspartate [NMDA]) can also cause a decrease in the ADC and cause cell swelling despite normal adenosine triphosphate (ATP) levels. This observation may suggest that a simple direct relationship, such as one in which the ADC decrease is directly correlated to tissue demise, may not be present. Nevertheless, human experience particularly shows that, in the absence of therapy for suspected acute cerebral ischemia, tissue with a low ADC value almost always progresses to infarction; therefore, the ADC value provides us with a powerful diagnostic tool.

The mystery deepens when we begin to consider how ADC changes with intervention. Our understanding here is most complete in animal models, in part because of the difficulty of examining humans with their widely varying pathologic conditions and in part because of the lack of effective therapies for most patients with stroke. We do know that, with early reperfusion, this decreased ADC value can normalize; this change reflects a normalization of the tissue energy status. Although, this normalization of ADC was initially thought to mean that the tissue was salvaged by reperfusion, both human and animal data have shown that this is not the case; infarcts can still often occur in tissue despite early reperfusion and normalization of diffusion and perfusion images. The phenomenon of infarction despite apparent normalization early after reperfusion is termed delayed injury or secondary injury. We knew that tissue with high signal intensity at DWI progressed to infarction, but now, the converse is clearly not always true; tissue that with a bright appearance at DWI that then becomes normal may or may not be salvaged from infarction. Because of this possibility, delayed or secondary injury is increasing scrutinized, and we are beginning to understand more about it with recent experimental results. For example, we know now that, although ADC values might normalize with acute reperfusion, metabolic imaging studies show that cerebral protein synthesis remains suppressed and abnormal. In short, this secondary injury is thought to involve failure of mitochondrial function, perhaps including apoptosis.

In this issue of *AJNR*, more evidence about secondary injury is presented (pages 180–188). Li et al document that, in a rat model of ischemia, 30 minutes of occlusion in the middle cerebral artery followed by reperfusion resulted in the normalization of ADC values, but histologic changes were persistent and severe; this finding confirms that of similar work done in animal models of hypoxia-ischemia. This result is important because it indicates that, although decreases in ADC values are associated with cellular swelling, the (pseudo)normalization of the ADC does not indicate normalization of cellular swelling and other forms of damage. Again, this observation confirms that the ischemic cascade may be a more difficult foe than we had hoped, and it suggests that, while decreases in the ADC are extremely valuable in the diagnosis of acute cerebral ischemia, the use of DWI to monitor therapeutic interventions such as thrombolysis may have some pitfalls. Because so few patients are currently receiving thrombolysis, the day-to-day effect of this point on most of our practices is, unfortunately, limited. However, it has important implications for the design of novel interventions, because early reperfusion and even normalization of energy balances clearly may not be enough to successfully treat acute ischemic stroke.

One message that these recent findings highlight—

one that goes beyond the specific topic of delayed injury in brain ischemia—is the important interplay between results in animal models and human findings. Certainly, the tremendous amount of work done in animal models, by groups all around the world, has vastly improved our understanding of acute cerebral ischemia. However, those conducting animal experiments have also learned from the human experience, and perhaps nowhere else are the shortcomings of seemingly good animal models so apparent as in the modeling of acute cerebral ischemia and its treatment. The best illustration may be the fact that more than 100 novel medications have been shown to be highly successful in the treatment of ischemia in animal models, and yet, each has failed to work in humans (2). Certainly. such experience highlights that, while animal models are essential, such models do not preclude careful clinical investigation–something to which we in neuroradiology are in an excellent position to contribute. Indeed, the observation of delayed injury after thrombolysis in humans seems to have sparked renewed interest in this area of study in animal models; an example is the work of Li et al in this issue.

In short, animal models have a lot to teach us, but our observations in the clinic remain extremely valuable. Such interplay between the clinic and the laboratory should encourage all of us interested in the care of patients with stroke to continue our communications with each other, because we each contribute our own piece of information to solving the mystery of how to treat acute cerebral ischemia.

A. Gregory Sorensen, MD
Department of Radiology
Massachusetts General Hospital
Boston, Massachusetts

References

1. Hoehn M, Nicolay K, Franke C, van Der Sanden B. **Application of magnetic resonance to animal models of cerebral ischemia.** *J Magn Reson Imaging* 2001;14:491–509
2. Kidwell CS, Liebeskind DS, Starkman S, Saver JL. **Trends in acute ischemic stroke trials through the 20th century.** *Stroke* 2001;32: 1349–1359

Sources of Variability in Measuring Carotid Stenosis on Time-Resolved Contrast-Enhanced MR Angiograms

The assessment of proximal internal carotid stenosis by using magnetic resonance angiography (MRA) has been substantially improved with the addition of time-resolved contrast-enhanced (CE) techniques. In this issue of the *AJNR*, Remonda et al (pages 213–219) report findings from a large clinical series in which two-dimensional (2D) digital subtraction angiography (DSA) was compared with time-resolved three-dimensional (3D) CE MRA for the evaluation of carotid stenosis. A total of 120 patients were enrolled in the study; 240 sets of carotid bifurcation images were available. The image data sets were randomly presented, and two observers measured the stenoses independently. The CE-MRA measurements were then correlated with the DSA measurements. The correlation was excellent, with an overall sensitivity of 98% and specificity of 96% ($P < .001$). The authors performed the investigation over a 2.5-year period, collecting a large amount of imaging data and conducting a retrospective analysis.The study is particularly important because of the large sample size.

A difficult problem for any CE-MRA study is the difference in spatial resolution between DSA and CE MRA. In this study, the in-plane resolution of the DSA images was described as follows: 1024 × 1024 matrix, 33-cm field of view, and 0.320 × 0.320-mm pixel size. By comparison, the time-resolved CE-MRA images were generated with an in-plane resolution of 1.0 mm × 1.5 mm, with a section thickness of 1.8 mm. Thus, the pixel size for the CE-MRA examination was 3–5 times that of the DSA studies.

Four separate CE-MRA image volumes were obtained during the passage of the contrast agent bolus. Each acquisition was approximately 5 seconds in duration. The 3D data sets were converted into 2D maximum intensity projections (MIPs) with orientations similar to those of the DSA images. Depending on the projection, the MIP images showed the vascular anatomy with a resolution varying from 1.0 × 1.5 mm in the coronal plane to 1.5 × 1.8 mm in the sagittal plane.

Although this spatial resolution is impressive, I would like to comment on the challenges of measuring proximal internal carotid stenosis from MIPs derived from time-resolved CE-MRA studies. Consider the following situation: DSA and CE MRA are performed in a symptomatic patient. The patient is found to have a 70% stenosis, by using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method. In this example, let us assume that the internal carotid artery distal to the stenosis measures 6 mm, and the residual lumen at the level of the stenosis measures 1.8 mm. By using the imaging parameters described by Remonda et al and by estimating the average resolution of the MIP image as approximately 1.5 × 1.5mm, the stenosis could be represented in three ways. If the stenosis is located near the center of one pixel, no partial volume effects would occur, and the stenosis would be correctly delineated. If the stenotic segment extends almost equally into two pixels, the signal intensity would be averaged over the two pixels, and each pixel would appear in the MIP image as part of the lumen. Thus, the lumen would be represented by two pixels instead of one. The resultant stenosis