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Diffusion-weighted imaging: to treat or not to treat? That is the question.

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radiologic findings also clearly point to a need for more careful and in-depth neurologic evaluations (eg, neurocognitive assessment, electroencephalography, evoked potentials) in patient populations previously considered "asymptomatic" in whom a neurologic problem may well exist. Such radiologic observations often supply food for thought to our neuroscience colleagues, who must dig deeper for the clinical answers to such questions. While the patient population is statistically small, the authors do demonstrate the value of sequential and longitudinal imaging observations in any patient population. The authors have done much to uncover the natural course by doing the study in a sequential manner.

Finally, this paper is an excellent representation of what we might and should hope to achieve in clinically relevant neuroimaging research in the future. No longer can we afford to focus only on the research and development of advanced applications and post-processing; rather, we must lead the way in putting such tools to good use by documenting and unraveling the complexity of our traditional anatomic observations. The authors' simple use of image segmenta-

tion to document their white matter observations in a sequential fashion was far more powerful than merely stating subjectively that there was or was not a change. Their use of spectroscopy was motivated not by "let's do it because we can," but by a specific effort to assess neuronal function and to search for discrepancies between evidence of neuronal dysfunction and anatomic changes in comparison with what was observed clinically. Their use of these tools has objectively strengthened their observations, and has paved the way for further study. All are important issues when patients may be hard to find, and stress the value of well-conceived investigations even with a limited number of patients.

WILLIAM S. BALL
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Diffusion-Weighted Imaging: To Treat or Not To Treat? That Is the Question

Diffusion-weighted MR imaging has been slowly but steadily evolving from a basic research topic to a clinical tool. Diffusion is an intrinsic physical characteristic of gaseous and liquid solutions reflecting the random, microscopic motion of molecules. It is measured in terms of the diffusion constant which, in general, increases in more dilute solutions and has a directional component. Early nuclear MR investigators appreciated that diffusion affected the MR signal. This observation was quickly followed by the development of MR methods to measure diffusion specifically. This technique has been applied to a wide variety of samples, from simple water solutions to

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complex gels to intact biological systems. While diffusion in biological systems often follows the principles of diffusion in simple solutions, there remain many unexplained phenomena related to the diffusional behavior of biological water.

As with nuclear MR, MR imaging is affected by molecular diffusion; techniques for diffusion-weighted imaging have been developed and applied to experimental animals and human subjects. One of the more interesting initial observations was that water diffusion varied under ischemic conditions. Somewhat unexpectedly, the diffusion coefficient of brain was found to decrease within minutes of onset of ischemia. Most diseased tissue is characterized by a

more "watery" state, with an associated increase in the magnitude of diffusion. Thus the decrease in diffusion in ischemic tissue offers the possibility of pathologic "specificity." In addition, ischemic diffusional changes occur much earlier than conventional T2 MR signal changes, suggesting greater sensitivity. Furthermore, under certain conditions, it was found that these ischemia-induced diffusion changes were reversible.

The obvious clinical implications of these observations were appreciated as early as 1990, and it was proposed that DWI would become an important tool for the evaluation of cerebral ischemia. But it is now 1998 and diffusion-weighted imaging is still not an established technique for evaluating clinical stroke. Why?

The answer relates to two problems—one technical, the other biological. Diffusion-weighted imaging has been more difficult to implement on clinical instruments than anticipated. Diffusion is a reflection of very small-scale motion; therefore, diffusion-weighted imaging must be very motion sensitive. Unfortunately, there are many other types of motion in the clinical environment, most of which are greater in magnitude than the subtle diffusional motion. The technical challenge of diffusion-weighted imaging has been to develop MR techniques sensitive to microscopic diffusional motion but not overwhelmed by blood flow, pulsating cerebrospinal fluid, and gross patient motion. Only recently have practical diffusion-weighted techniques been clinically demon-

strated, as nicely represented by the article by Lövgren et al in this issue of *AJNR*. It now seems that the technological challenge has been met.

The second problem has been the biomedical significance of the diffusion-weighted signal changes: are they indicative of irreversibly injured tissue (infarct) or do they reflect reversibly ischemic tissue (tissue at risk of infarct)? The answer determines the role of diffusion-weighted imaging in the management of acute cerebral ischemia.

Until the recent FDA approval of alteplase (rTPA) for intravenous fibrinolytic treatment of acute cerebrovascular thrombosis, there was little, if any, active management of acute, nonhemorrhagic stroke. Therefore there was little imperative to develop any new imaging technique, including diffusion-weighted imaging, as patient treatment would not be affected. Though the situation has changed with the advent of alteplase; the role of diffusion-weighted imaging remains unclear, partly because of incomplete understanding of the biological significance of ischemia-related diffusion changes and partly because of the generally undefined role of imaging in directing stroke therapy. According to the package insert, the only role of imaging in the alteplase treatment of acute stroke is the exclusion of major intracranial hemorrhage, a task easily performed with CT. However, it must be remembered that the National Institute of Neurological Disorders and Stroke study, which led to FDA approval of alteplase, demonstrated only a mild improvement in long-term clinical outcome, which was partially offset by increased short-term morbidity and mortality secondary to drug-related hemorrhage. Many investigators, myself included, suspect that clinical outcomes from alteplase, as well as other acute stroke therapies, could be improved with better patient selection. Fibrinolytic treatment of patients who do not have vascular occlusive disease isn't likely to help. Likewise, patients with already completed major stroke might not benefit from any therapy and might actually be harmed by therapeutic side effects or complications, such as hemorrhage. The European Cooperative Acute Stroke Study of alteplase treatment of acute stroke indeed revealed a subgroup of patients with poor

outcomes, which in retrospect showed subtle CT changes of major infarction on the pretreatment scan. More advanced imaging is likely to improve triage of acute stroke patients into appropriate treatment (or nontreatment) groups.

What is needed is a diagnostic modality that identifies not only infarcted tissue (that need not be treated) but tissue at risk of infarction (that might benefit from appropriate treatment). It is now critical to understand the clinical significance of diffusion-weighted signal changes: do they reflect infarcted tissue, which might be used as a contraindication to therapy, or do they reflect tissue at risk of infarction, which might be used as an indication for treatment? Prior animal experiments suggested the former possibility; recent clinical results better support the latter.

Based on the currently popular theory that the diffusion-weighted signal changes reflect failure of cell membrane ionic pumps and subsequent redistribution of intracellular and extracellular water, I suspect that the diffusion-weighted signal changes usually reflect irreversible injury. Prior ^{31}P nuclear MR experiments generally showed that there was a very narrow (and relatively low) range of ischemia under which brain adenosine triphosphate (ATP) was reduced. In general, ATP in ischemic brain remains normal or essentially disappears, indicating cell death. Assuming very tight coupling between ATP levels and ATP-dependant pump function, it is likely that there is a correspondingly narrow range of ischemic conditions under which diffusion-weighted signal changes are reversible. However, this is speculation; now that we have more widely available, clinically practical diffusion-weighted imaging techniques, it is critical to apply them more broadly to patients with acute stroke to understand better the clinical implications of the findings. This understanding will then direct the appropriate incorporation of diffusion-weighted imaging into acute stroke treatment protocols.

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