The Clinical Relevance and Scientific Potential of Ultra High-Field-Strength MR Imaging

As neuroradiologists, we are fortunate to work with the ever-advancing MR imaging technology. MR imaging has evolved as a robust and highly versatile clinical tool. In addition, MR imaging has caused dramatic changes in the clinical evaluation of a host of neurologic disorders; a well-recognized example is the role of diffusion-weighted imaging in acute stroke. Such advances typically stem from discoveries of phenomena rendered visible by the development of new MR imaging methods.

Unfortunately, not every new scientific observation or technologic development is associated with the impact and significance that diffusion-weighted imaging has had on the study of stroke. As critical readers of the scientific literature, radiologists should judge the technical accuracy and scientific soundness of a new observation or imaging method. This process involves critical thinking (1). As medical practitioners, we have to ascertain potential clinical relevance of new imaging technology. Then, we need to consider which patients would benefit most and what effect, if any, the new information may have on our future clinical practice. Finally, in cases in which a medical procedure or technology is associated with high cost or health risk, more refined judgment is required to integrate clinical benefits and scientific facts as well as to minimize cost and patient risk.

In this issue of the *AJNR*, Christoforidis et al present a means of direct visualization of abnormal microvascularity within glioblastoma multiforme by using 8-T MR imaging. By using a 2D gradient-recalled echo sequence to obtain 2-mm axial sections of the brain, these investigators were able to produce images of a brain tumor with an in-plane pixel size of 222 μ (by using a matrix of 900 $\times$ 900 and a 20-cm field of view). The resulting images displayed normal transmedullary veins that are invisible at conventional angiography. They also showed zones of increased microvascularity (corresponding to tumor blush on conventional angiograms) that are invisible at 1.5-T T2-weighted fast spin-echo MR imaging. In an attempt to underscore the significance of this finding, the authors cite animal models of tumor angiogenesis in which "apparent vessel density" on high-spatial-resolution MR images correlates with histopathologically identified density of microscopic blood vessels.

To address clinically driven questions, critical readers should note the following issues. First, the diagnostic significance of microvascularity alone in the histopathologic evaluation of glioblastoma multiforme is somewhat limited; there are four major grading criteria, of which neovascularity is only one. Second, the therapeutic significance of these findings is unclear; the elimination of neovascularity by various treatments does not necessarily make recurrence of glioblastoma multiforme less likely. In addition, the zones of microvascularity seem to consist mainly of small veins; therefore, the relevance to intraarterial chemotherapy is not clear. Third, the scientific significance seems to be related to angiogenesis, about which much has been written in recent years. However, further work needs to be conducted to determine the correlation of abnormal microvascularity with histopathologically established neovascularity, and to measure the success rate of ultra high-field-strength MR imaging in identifying microvascular changes in a series of glioblastoma cases (as opposed to those changes found in association with other brain tumors).

The issue of technical significance takes us from the clinically driven questions to those related to how a new technique should be applied. These technical issues raise some of the most interesting questions. Compared with a 1.5-T MR imaging system, an 8-T MR imaging system boosts the signal-to-noise ratio (S/N) by a factor between 3 and 5. (This factor depends on various technical parameters, including whether the 8-T MR imaging system uses stronger gradients and increased bandwidth, both of which may reduce S/N gains) (2). This technical advantage offers the possibility of performing various MR imaging experiments even beyond the pursuit of maximal spatial resolution. Unfortunately, technical problems can render whole-brain MR imaging much more problematic at 8 T than at 1.5 T. These problems are related to substantial artifacts due to B_0 inhomogeneity, heightened magnetic susceptibility, inhomogeneous radio-frequency field (B_1), and radio-frequency eddy currents (2, 3). For the sake of brevity, let us assume that engineering and scientific advances can solve these technical problems in the near future. Then, radiologic scientists will have the luxury of using the 8-T MR imaging system in many ways.

We may optimize MR pulse sequences that are adequate at 1.5 T but are constrained by physical or physiological limits in signal generation. Functional MR imaging at 1.5 T with blood oxygenation level–dependent effect from a specific task activation often results in a mere 1% to 2% signal intensity change. Compare that with a conservative estimate of 3% to 6% signal intensity change at 8 T. Similarly, diffusion and perfusion MR images are typically obtained at low spatial resolution to maximize acquisition speed. For these MR pulse sequences, the much higher field strength offers the opportunity to collect imaging data at even smaller time intervals (ie, greater temporal resolution) or with smaller imaging voxels (ie, greater spatial resolution).

Experiments can be performed at 8 T that would be extremely challenging at 1.5 T. This includes heteronuclear MR imaging, such as with phosphorus MR spectroscopy and sodium MR imaging, both of which are feasible at 1.5 T but generally require a prolonged pulse sequence to ensure satisfactory signal acquisi-

tion. Both of these technologies have been explored in animal models but have yet to make a notable impact in the clinical realm. As has been touted elsewhere, phosphorus MR spectroscopy may yield significant information regarding cellular energy metabolism, and sodium MR imaging may provide detail regarding the integrity (or lack thereof) of physiologically excitable cells, such as neurons.

Surface coil technology and ultra high-field-strength MR imaging could be combined to perform MR microscopy to detect otherwise invisible structural abnormalities in cerebral cortex. Although this could be used to visualize even finer microscopic detail within well-defined lesions, such as those in glioblastoma multiforme, another strategy is to study neurologic disorders associated with structural lesions that are difficult to visualize on conventional MR images. One example is the imaging of pediatric epilepsy; the use of optimized, high-spatial-resolution techniques at 1.5 T without surface coils (4) or with surface coils (5) has improved the detection of focal cortical dysplasia, a lesion that often is surgically treatable. It is likely that MR microscopy will further improve our ability to discern the subtle cortical abnormalities associated with focal cortical dysplasia. From a clinical viewpoint, MR microscopy offers greater promise in identifying hard-to-find structural lesions that are treatable than in demonstrating the fine ultrastructural detail of lesions that are not treatable; the latter remains merely academic, unless the discovery leads to a cure.

Another approach is to use the 8-T MR imaging system as a time-saving device that facilitates the construction of an MR imaging database that combines structural and functional neuroimaging data. Scientists could obtain a battery of imaging data from patients by performing a multiple-sequence MR imaging study. This approach is rendered feasible by using the increased S/N to save imaging time during the longer and more complex MR pulse sequences (eg, MR spectroscopy), thereby enabling an increase in the number and types of pulse sequences. For example, a single MR imaging examination could include structural imaging, diffusion and perfusion MR imaging, proton MR spectroscopy, visual functional MR imaging, and heteronuclear MR imaging. This imaging database could be useful in several contexts. One possibility is an in vivo study of neurobiologic changes throughout the human life cycle, coupled with the development of multidimensional, graphic displays of structural and functional imaging data sets. Comparison of new with old images could be facilitated by computer-driven video displays of time series imaging data sets.

Major scientific benefits are possible with use of the ultra high-field-strength MR imaging system. Developing the full potential of an 8-T MR imaging system is likely to require significant technical advances and continual problem solving, similar to what was needed in the early days of the 1.5-T MR imaging systems. In evaluating potential clinical benefits of 8 T, it should be noted that the technology currently available on commercial 1.5-T MR imaging systems is sophisticated and is much further developed than the most advanced 0.35-T MR imaging systems of the 1980s. Also, 3- and 4-T MR imaging systems are under development that will be less severely affected by technical artifacts related to higher field strength. Therefore, the incremental clinical benefits obtained in moving from a field strength of 1.5 T to 8 T are likely to be less dramatic than those achieved 15 to 20 years ago when the giant step from 0.35-T to 1.5-T MR imaging occurred. More research is required to establish the potential clinical benefits of the ultra high-field-strength MR imaging system; this work may be facilitated by the use of various imaging strategies that judiciously apply the system's technical advantages to the solution of clinical problems that are potentially treatable.

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Toward an Evidence-Based Approach in the Management of Concussion: The Role of Neuroimaging

Considerable debate centers on whether any single symptom or sign may serve as a better indicator of severity of brain injury in cases of concussion. Few prospective radiographic studies on longitudinal volumetric quantitative analysis of brain mass loss appear in the literature, particularly in association with specific posttraumatic symptoms or signs after mild or moderate head injury (1). Noninvasive radiographic tests, such as

CT, MR imaging, single photon emission CT, and positron emission tomography, can provide clinically meaningful information regarding both anatomic and biochemical changes that may occur in the brains of patients with postconcussion symptoms. This information, and the results of sensitive neuropsychological tests, may have important applications in the future medical management of concussions. Presently published guidelines regarding the medical management of sports-related concussions (2) and the management of concussions in the emergency department (3) rely heavily on expert opinion and anecdotal case reports. Evidence-based information is needed to validate current concussion management guidelines.

In this issue of the *AJNR*, Mackenzie et al (page XXX) report the findings of a longitudinal quantitative analysis of brain atrophy in cases of mild and moderate closed head injury. They used an MR-derived measure of brain parenchyma volume to assess differences between a control group and a posttraumatic head injury group based on serial MR images obtained over time. The results of their study suggest a statistically significant decline over time in the percent of brain parenchyma volume in the trauma group compared with that in the control group. Furthermore, brain atrophy was shown to be significantly greater in patients who had loss of consciousness at the time of trauma than in those who did not. The authors also suggest that initial Glasgow Coma Scale scores were not effective predictors of extent of brain atrophy in the mild to moderate closed head injury group. These results have important implications that, if validated in a well-controlled study in a large number of subjects, could alter current definitions of brain injury severity and possibly alter current guidelines and recommendations regarding the management of concussions. In addition, these results may help to explain the unexpected persistence of postconcussion symptoms in a small population of patients with mild traumatic brain injury. Neuroimaging studies, such as that presented by Mackenzie et al, can play an important role in answering the question of whether current measures of brain injury severity have poor sensitivity, specificity, and precision.

Assessment of the severity of brain injury facilitates determination of the prognosis for recovery, as well as the management of the injury. The usual criteria for the assessment of brain injury severity at the time of trauma include the Glasgow Coma Scale score, the duration of posttraumatic amnesia, and the duration of loss of consciousness (4). Neuroimaging findings presently do not play a role in the classification of brain injury severity. Conventionally, brain injuries are classified as mild, moderate, or severe on the basis of these measures. For example, "mild traumatic brain injury" has been defined as head trauma with a Glasgow Coma Scale score of or more than 13, with a posttraumatic amnesia duration of less than 24 hours, and with loss of consciousness, if any, of less than 30 minutes (5). The term *mild traumatic brain injury* is misleading as a diagnosis, because it includes a spectrum of manifestations that can range from transient mild symptoms to ongoing disabling problems. This definition sets an arbitrary boundary between the classification of a mild traumatic brain injury, presumably with a benign prognosis, and a moderate brain injury. A continuum of progressive brain injury severity exists in terms of pathologic findings and associated clinical signs and symptoms. Pathologic features that may correlate with traumatic brain injury severity that are not included in the conventional classification criteria may include the location and extent of cortical contusions, intracranial hemorrhages, axonal shear injury, and skull fractures. It has been shown that those patients having mild traumatic brain injury with unilateral or multifocal brain lesions shown on CT scans or MR images are more likely to have neuropsychological symptoms after trauma (6, 7). This emphasizes the need to rethink the classification criteria of brain injury severity.

Concussion is a word often used in the medical literature as a synonym for mild traumatic brain injury. Concussion is the most frequent traumatic brain injury treated by clinicians. It has been estimated that 80% of head injuries involve concussion, or mild traumatic brain injury. The physician's responsibilities in assessing the condition of a patient with a concussion include determining the need for emergent intervention and, in the case of an athlete, offering guidance regarding the ability to safely return to sports play. Concussion may be complicated by cortical contusions, skull fractures, cerebral edema related to the second impact syndrome, intracranial hemorrhage, neuropsychological deficits, and postconcussion syndrome. The risk for complications associated with concussion is increased in those with prolonged loss of consciousness or posttraumatic amnesia or in athletes who prematurely return to sports play. Clinical management guidelines have been developed to assist physicians in the management of concussion. These guidelines, including recent ones published by the American Academy of Neurology (8) and the American Academy of Pediatrics/American Academy of Family Physicians (3), have increased awareness of signs, symptoms, and potential sequelae associated with concussion. However, these guidelines rely heavily on expert opinion and anecdotal case reports. Definitive, evidence-based information is therefore needed to validate current recommendations. MacKenzie et al suggest the importance of loss of consciousness rather than the Glasgow Coma Scale score as a predictor of outcome in cases of mild and moderate closed head injury. Also, they raise the possibility of a trauma-induced apoptosis as a cause of brain atrophy, which may result in the persistence of postconcussion symptoms in a subpopulation of the mild to moderate brain injury group. Ultimately, neuroimaging studies such as those presented by MacKenzie et al, in conjunction with clinical and neuropsychological data, will help to provide the evidence-based information that is needed to clarify current concussion management guidelines and also to clarify the conventional definitions of mild, moderate, and severe traumatic brain injury.

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