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Differentiation of Benign versus Pathologic Compression Fractures with Diffusion-weighted MR Imaging: A Closer Step Toward the "Holy Grail" of Tissue Characterization?[1]

The feasibility of diffusion imaging with magnetic resonance (MR) imaging (1–3) and its clinical potential in neurologic disorders (4) were demonstrated more than a decade ago. Substantial technical progress has allowed diffusion imaging to be performed with clinical MR units, with minimal artifacts, especially in the brain. The development of diffusion imaging represents a landmark contribution in the history of MR imaging. Molecular diffusion refers to the general, thermal, random displacement of molecules. During typical MR imaging encoding times, water molecules diffuse at distances on the order of a few micrometers. Diffusion MR imaging is thus exquisitely suited to probing the structure of biologic tissues at a microscopic level well below the typical resolution of MR images, which remains at the millimeter scale.

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See also the article by Baur et al (pp 349–356) in this issue.

The measurement of molecular displacements in biologic tissues has enormous clinical potential—from determining the orientation of white matter fibers in the brain to monitoring laser surgery. Perhaps the most striking application, however, has been in acute brain ischemia. The early finding in an animal model (5) that water diffusion is substantially lower in ischemic regions has become a clinical reality in just a few years, following initial reports about clinical stroke (6–9), and promises to revolutionize the treatment of patients with stroke. Diffusion-weighted MR imaging can readily depict cytotoxic edema associated with acute brain ischemia, within minutes of the ictus, as an area of slow, decreased diffusion that appears as an increase in signal intensity. With an "imaging package" that includes diffusion- and perfusion-sensitive MR imaging and MR angiography, clinicians have in their hands a set of invaluable tools for helping them diagnose stroke at a very early stage (when tissue is still salvageable), evaluate the severity and extension of the ischemic region, assess new therapeutic (pharmacologic or interventional) strategies, and follow up disease (in both the acute and the chronic phases) (10). Of course, MR imaging systems must first be made available to patients outside the emergency room, or patients must be brought to the emergency room within a few hours; this remains a formidable challenge.

Another important field of application has been brain white matter, where diffusion has been shown to be highly anisotropic: Diffusion is markedly decreased when the myelin fiber tracts are perpendicular to the direction of the magnetic field gradient used to measure diffusion (11). On diffusion-weighted MR images, white matter tracts where fibers are perpendicular to the gradient direction have high signal intensity. Conversely, fibers that are parallel to the gradient direction have low signal intensity. The actual direction in space of the white matter bundles can indeed be fully determined by using the "diffusion tensor imaging" method (12). Recent work has demonstrated the feasibility of using diffusion tensor imaging in the human brain (13). Myelin fiber orientation mapping may be useful to better understand white matter diseases such as multiple sclerosis, Wallerian degeneration, delayed white matter myelination in neonates or, more generally, any white matter disease. In cognitive neuroscience, mapping of white matter fibers that tie activated cortical regions may provide an important step toward the concept of "functional connectivity."

Feasibility studies have also explored the potential of diffusion imaging in muscle, heart, liver, and kidney. Now, the article by Baur et al (14) in this issue of *Radiology* points toward a new field of application: bone marrow. By using diffusion-weighted MR imaging, the authors have successfully addressed a common dilemma in clinical radiology: the difficulty in differentiating benign vertebral compression fractures from those due to an underlying malignancy. In their preliminary study of 39 vertebral compression fractures in 30 patients, all benign vertebral fractures were hypo- to isointense to adjacent normal bone marrow on diffusion-sensitized images, and all pathologic compression fractures (from very different primary neoplasms) were hyperintense to normal bone marrow. Conversely, the imaging charac-

teristics of both benign and malignant compression fractures at conventional spin-echo and short inversion time inversion-recovery, or STIR, imaging were variable and overlapped.

MR imaging can be sensitized to diffusion by inserting gradient pulses into any imaging sequence (15). Without additional gradients, typical MR imaging sequences have intrinsically very low diffusion sensitivity so that diffusion effects are completely negligible. Because the smallest detectable length of molecular diffusion paths is primarily determined by the intensity of the gradient pulses, there is a need to use hardware capable of providing stable gradient pulses of the utmost intensity. This requirement may be extremely challenging when considering whole-body instruments designed for clinical studies. In the past, the specifications of clinical MR imaging units made it difficult to obtain reliable diffusion images. Acquisition times were long (10–20 minutes), and the presence of the large diffusion gradient pulses required for diffusion made the images very sensitive to macroscopic motion artifacts (eg, those induced by involuntary or voluntary motion, breathing, or cardiac-related pulsation). Demonstrative clinical studies have started only very recently, when better MR imaging units equipped with echo-planar imaging capabilities became available. With "single-shot" echo-planar imaging, it is possible to acquire an image in a few tens of milliseconds and to image the entire brain in less than a second, virtually freezing macroscopic motion (16,17). The principles of echo-planar imaging were established in the 1970s, but its implementation with clinical MR imaging units was delayed until the early 1990s due to the special hardware necessary, as large gradient pulses must be switched very quickly. Many commercial MR imaging systems can now be upgraded to perform echo-planar imaging. This enhanced gradient hardware also provides increased gradient strength for diffusion, thus improving sensitivity to diffusion (15). Echo-planar imaging is also certainly the best method for quantifying diffusion, because diffusion and relaxation effects contribute separately to the MR imaging signal and can be easily separated.

On diffusion images, diffusion values are displayed by using a gray scale, where high signal intensity corresponds to high, fast diffusion and low signal intensity to low, slow diffusion. Some investigators, however, have proposed that we limit diffusion studies to the analysis of the raw images obtained with some degree of diffusion sensitivity or weighting. For this reason, these images are called diffusion-weighted images, as in the study by Baur et al. The contrast on these images is opposite that found on true diffusion images: Regions with high diffusion have more pronounced MR signal intensity and appear dark, whereas regions with low diffusion appear bright. Diffusion-weighted imaging may be convenient, but one has to be aware that the content of the image is affected by many parameters other than diffusion because they are also usually strongly T1 and T2 weighted. Because these parameters may not have the same behavior as with diffusion, variations in image intensity may be difficult to interpret. Whenever possible, absolute diffusion imaging must be preferred; echo-planar imaging is the best method for achieving this goal. Indeed, it is important to notice that diffusion imaging is a truly quantitative method. The diffusion coefficient is a physical parameter that directly reflects the physical properties of the tissues in terms of the random movement of translation of the molecules under study. The diffusion coefficient thus does not depend on the field strength of the magnet or the pulse sequence used, which is not the case for other classic MR imaging parameters (eg, T1 or T2 relaxation times). Diffusion coefficients obtained at different times in a given patient, in different patients, or in different hospitals can be compared without the need for normalization.

Unfortunately, some problems remain with echo-planar imaging, such as limited spatial resolution, sensitivity to eddy currents and local susceptibility gradients, and chemical shift, that may result in severe geometric distortion and signal dropout, especially at interfaces between tissues, air, and bones. One can partially overcome these limitations in the brain by using "multishot" echo-planar imaging with cardiac gating and navigator echoes (18,19); however, these constraints are even more substantial in the body and prevented Baur et al (14) from using echo-planar imaging in their study. As a matter of fact, to our knowledge echo-planar imaging has not yet been used very successfully in the spine. In the study by Baur et al, diffusion-weighted imaging was performed with a time-reversed fast imaging sequence based on steady-state free precession (SSFP). The possibility of sensitizing this particular MR imaging sequence to diffusion was demonstrated long ago (20,21), but it was fast made clear that quantification of diffusion by using SSFP-based sequences was difficult, as one could not remove confounding relaxation effects (ie, the effects of T1, T2, and diffusion could not be clearly separated as with spin-echo–based sequences such as echo-planar imaging) (22). Therefore, images must be interpreted with caution because one cannot infer that observed signal intensity changes are solely related to diffusion. Furthermore, the degree of diffusion sensitization with this sequence is difficult to appreciate.

The degree of sensitivity to diffusion is generally described by the so-called b factor (4), which takes into account the intensity and timing of the gradient pulses. This b factor can be somewhat compared with the echo time of an MR imaging sequence to depict its degree of T2 weighting. By using a phantom, Baur et al estimated the b factor of their sequence as 165 sec/mm^2, which is a rather low value for diffusion imaging (adequate values on the order of 1,000 sec/mm^2 have been suggested for cerebral diffusion imaging). With such low values, only fast diffusion can be seen. The authors overcame the technical shortcomings of their approach by showing in a subgroup of patients that a clear distinction between benign and malignant fractures was visible only when the diffusion-sensitizing gradient pulse was present. In fact, the hypointense signal observed in benign fractures was seen only with the diffusion-weighted sequence, which is suggestive of increased water mobility. The hyperintense signal observed in malignant vertebral compression fractures, however, was present with and without the diffusion-sensitizing gradient and may not be related to a decrease in diffusion. Much larger b factor values would have been necessary to check this point. A b factor of 600 sec/mm^2 was used in another subgroup of patients, not included in the study, and apparently did not yield additional information.

Indeed, the relationship between the observed diffusion effect and the actual molecular displacement behavior is not straightforward (23). Water diffusion in most biologic tissues is generally much lower than that measured in pure water. This discrepancy must, therefore, be related to the structure of the biologic medium itself. The reduction of the diffusion coefficient may result from compartmentation, with water molecules encountering barriers that prevent them from diffusing freely—whether those barriers are permeable or not. The diffusion path may also be lengthened by the presence of obstacles, or water molecules may be retained by attractive centers or surfaces. In any case, water molecules will "sense" all these ob-

stacles during the time over which diffusion is measured (the so-called diffusion time).

Perhaps the most powerful concept formulated to date to explain the low diffusion values found in biologic tissues is that of "tortuosity," a concept that has been widely used in solid porous media studies and, more recently, the brain (24,25). The idea behind tortuosity is that, because of the presence of obstacles (eg, cells, fibers, macromolecules, organelles), water molecules must travel longer paths to cover any given distance. In other words, molecules cannot travel in a "straight" path but must diffuse around structures that are more or less impermeable to them. This situation results in a longer time to travel or an apparent decrease or slowdown in diffusion. It is interesting that this diffusion reduction can be modulated by the geometry of the tissue. For instance, it has been hypothesized that the decrease in diffusion in brain ischemia could be ascribed to the cell swelling associated with cytotoxic edema, which reduces the size of the interstitial space and increases tortuosity (26). Hence, the rationale followed by Baur et al was that the free mobility of water in interstitial tissue could differ in bone marrow according to the underlying abnormality. Acute benign fractures with an increase of the interstitial space in relation to edema or hemorrhage would have increased water mobility, whereas a compact accumulation of tumor cells in pathologic vertebral compression would reduce the interstitial space and water mobility. On diffusion-weighted images, this would translate to a decreased signal intensity for benign fractures and an increased signal intensity for fractures of malignant origin; this was observed by Baur et al. This hypothesis is quite original and interesting but, of course, needs further confirmation with proper quantitative analysis.

The general problem of tissue characterization is certainly a "Holy Grail." One must remain cautious, however, because MR imaging is a macroscopic technique, and only microscopic approaches can really enable the assessment of malignancies, which may exist only in a very limited number of cells (at least at the initial stage) and, thus, might not be visible with imaging. Although the interpretation proposed by Baur et al is compatible with their findings, from a biophysic mechanism standpoint, it remains to be seen whether the decrease in diffusion would be observed with any kind of malignant tissue. Cell proliferation may not be large, and the tumoral tissue may include a mixture of regions with edema. As a matter of fact, opposite results have been found in the brain, as the most malignant tumors had the highest diffusion coefficients (15). It remains that the presented results are impressive. Diffusion-weighted MR imaging might enable the differentiation of benign from malignant compression fractures, offering great potential in the treatment of patients with vertebral compression fractures. This is an exciting finding that could dramatically change the clinical outcome in a very large number of patients.

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