

Diffusion/Perfusion MR Imaging of the Brain: From Structure to Function¹

CONSIDERABLE interest has recently emerged in the capability of magnetic resonance (MR) to image and measure molecular diffusion and capillary flow or perfusion. Sessions on diffusion/perfusion imaging are now common at major MR imaging meetings, and the number of publications related to this topic is rapidly growing. This interest has been triggered by the important clinical potential of diffusion/perfusion imaging and also by the controversies that still exist in its technical achievement, mainly regarding perfusion measurement. The excellent article by Chenevert et al (1) in this issue has the merit of addressing both issues.

Diffusion/perfusion imaging relies on the well known sensitivity of MR to spin motion in the presence of magnetic field inhomogeneities. Motion thus represents a "natural" marker of the MR signal, so that no external contrast material is theoretically needed. In this respect, diffusion and perfusion are often confounded. Indeed, diffusion and perfusion refer to different physical phenomena and present different technical challenges. While perfusion can be better evaluated today by many methods excluding MR imaging, the choice of MR imaging to measure diffusion *in vivo* is almost a necessity.

Measuring molecular diffusion in tissues presents several potentially useful approaches to tissue characterization for functional studies, from the determination of cell geometry to the early

clinical evaluation of stroke. This interest in diffusion results from its unique link to molecular mobility. Unlike T1 and T2, diffusion is *not* an MR parameter; that is, diffusion is defined outside of the MR context and does not depend on the MR environment, such as the strength of the magnetic field. However, MR is the unique tool that allows the noninvasive measurement of diffusion directly from the molecular displacements. Water in tissues has a diffusion coefficient that is two to three times less than that of free water (2). This is largely explained by the high viscosity of bulk water in tissues due to the presence of large molecules such as proteins in intracellular spaces. Tissues (normal or abnormal) with different viscosities or a different balance between intra- and extracellular water might thus present different diffusion coefficients, which are the source of contrast in diffusion images.

On the other hand, the diffusion excursion range of water molecules during typical MR measurement times (100 msec) is on the order of a few microns, within the size range of a cell. Water diffusion is thus a useful marker of tissue structure at a microscopic level much too small to be observed directly with most current clinical MR imaging methods. For instance, the presence of obstacles to diffusion (eg, cell membranes, fibers, or intracellular organelles) results in measurable impeded or restricted diffusion effects. Due to the reduced range of possible displacements, the diffusion coefficient is apparently reduced compared with that of free water (3). This effect has been shown in vegetable tissues (4), in which the cell wall is essentially impermeable to water transport, or in measuring diffusion of metabolites that remain inside the intracellular compartment (5). In living animal tissues, however, cell membranes are more or less permeable to water, and restricted diffusion effects may not be as sharply visible.

Furthermore, the degree of hindrance or restriction may not be the same for different directions of motion, so that the measured diffusion coefficients may vary with the direction of measurement (anisotropic diffusion). Examples have been shown in muscle

(6) and recently in cat brain white matter (7). Chenevert et al have now confirmed these results in the human brain white matter, as was suggested by Thomsen et al (8). Diffusion coefficients are significantly decreased when the myelin fiber tracts are perpendicular to the direction of the magnetic field gradient used to measure molecular displacements. Water diffusion in gray matter does not exhibit anisotropy, and it is tempting to ascribe the white matter diffusion anisotropy to the fibers themselves, so that diffusion imaging could be used for three-dimensional mapping of myelin fiber orientation.

However, as Chenevert and colleagues point out, it remains that the exact origin of this anisotropy is not clear. A simple model may assume that water displacements across the axon diameter are confined in the axonal spaces by the myelin sheath complex. When diffusion measurements are made parallel to the direction of the fibers, diffusion is much less restricted, resulting in higher measured diffusion coefficients. Indeed, the situation is much more complex, as it has been shown that the myelin sheath is somewhat permeable to water (9). The reduced value of the diffusion coefficient across myelin fibers could thus only reflect a decreased water mobility through the successive lipid layers. On the other hand, the enhanced value of diffusion measured parallel to the axoplasm could arise from a facilitated transport favored by the highly oriented intraaxonal microstructures, such as microtubules or microfilaments, in relation to axoplasmic transport. Thus, the measurement of anisotropic diffusion in white matter may offer several exciting applications and could provide valuable information on white matter diseases, such as multiple sclerosis or abnormal white matter development, in neonates and children.

Another promising application is suggested by the ability of diffusion imaging to demonstrate a stroke at a very early stage. Moseley et al (10) have recently shown that the diffusion coefficient of water is significantly decreased within minutes following an ischemic insult, while all other imaging techniques, including conventional

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¹ From the Diagnostic Radiology Department, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, MD 20892. Received August 10, 1990; accepted August 14. Address reprint requests to the author. © RSNA, 1990

See also the articles by Chenevert et al (pp 401-405) and Turner et al (pp 407-414) in this issue.

MR imaging, fail to show any change. This decrease in diffusion could reflect a modification of the water balance in the tissue, possibly due to the massive entry of ions and accompanying water into the intracellular space following the failure of the ionic transmembrane pumps (cytotoxic edema). At a later stage (subacute ischemia), when abnormalities are seen on conventional MR images (increase in T2), the diffusion coefficient increases well above its normal value and is probably associated with vasogenic edema. Diffusion imaging thus offers the unique opportunity to address, noninvasively and in a clinical setting, fundamental issues about the response of brain tissue to stroke at different stages, with potentially important clinical implications. Early detection of stroke, at a stage when tissue damage is still reversible, may justify the use of more aggressive reperfusion or nervous tissue protection therapies.

Although, until now, only much more modest results have been obtained by using diffusion imaging in a clinical context (11-13), diffusion contrast clearly appears different than T1 or T2 contrast. Further work remains to fully understand the clinical significance and the usefulness of this new source of contrast.

Perfusion, however, is a more technically challenging parameter. There are already several widely used and established methods other than MR imaging to measure perfusion (blood flow) in a clinical setting. Most non-MR imaging perfusion techniques use tracers or contrast agents. In that sense, MR imaging perfusion methods based on non-proton nuclei or contrast agents (gadolinium or dysprosium chelates) (14) are not drastically different from them. MR imaging methods can be useful if they demonstrate better spatial or temporal resolution or if they are easier, safer, or cheaper to use than non-MR techniques. On the other hand, MR imaging perfusion methods using gradient sensitization rather than contrast agents represent a fundamentally different approach. Classically, perfusion is quantified in terms of milliliters of blood delivered per minute per 100 g of tissue. Now perfusion can be quantified in terms of capillary density (milliliters of circulating blood per 100 g of tissue) or average blood velocity (millimeters per second) (12). These param-

eters may bring new insights to micro-circulation physiology not available from current techniques. For instance, it can be determined whether the blood velocity or the capillary volume is involved when blood flow changes in physiologic or pathologic conditions.

That is why, despite important technical difficulties, perfusion MR imaging with gradient sensitization may prove useful and a source of important progress in our understanding of normal or abnormal tissue function. Work remains to characterize the way capillary blood flow is seen with use of these techniques and to fully establish their reliability in obtaining accurate, reliable, and reproducible data, which is impeded by the extremely small volume fraction occupied by flowing blood. Necessary requirements are high signal-to-noise ratios, which can be achieved by grouping pixels in regions of interest, and extremely good gradient hardware, especially regarding gradient power, stability, and eddy currents.

The other problem is to overcome "macroscopic" motion of tissues, a source of major artifacts. In this respect, the ingenious technique proposed in this month's issue by Chenevert and coworkers is very efficient at the price of limited field of view and can be implemented on most clinical imagers. However, a major step toward the future of diffusion/perfusion imaging is certainly to use echo-planar or single-shot imaging techniques, which are capable of motion freezing and providing many images in short time intervals, as proposed in this issue by Turner et al (15).

With such improvements and more to come, imaging of brain activity as it varies according to physiologic or pathologic conditions could become feasible. Despite low spatial resolution, variations in cerebral blood flow with external stimulations have been shown with positron emission tomography. It would be fascinating to obtain such results without tracer or ionizing radiation in normal or abnormal conditions, such as in patients with Alzheimer disease or psychiatric disorders, by using the high spatial and temporal resolution of perfusion MR imaging. ■

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