See related article, p 2962.

I can’t change the laws of physics!” Inflected with the appropriate Scottish brogue, this quote brings to mind a character from a well-known classic science fiction television series. However, Scotty’s lament might be that of the clinical MR spectroscopist as well, for there are few areas in medical diagnostic imaging in which the immutable laws of physics pose such direct constraints. In selecting an in vivo spectroscopy protocol, spectral quality (as measured by signal-to-noise ratio), spatial resolution, spatial coverage, examination time, and the minimum time to obtain a spectroscopic imaging series are inextricably entwined. Optimization of one parameter necessitates a compromise elsewhere. For instance, improvement of the spatial resolution of a MR spectroscopic imaging (MRSI) series can be achieved, but at the expense of a longer acquisition time and/or reduced signal-to-noise resolution of the spectra. The laws of physics will not have it otherwise.

Although the first in vivo 1H spectrum from the brain of a patient poststroke was reported almost 25 years ago,1 followed a few years later by 1H spectroscopic imaging in one2 and 23 dimensions, the difficulty of obtaining good-quality MRSI from patients after stroke, especially in the acute phase, has been one of the factors limiting the more widespread application of MRSI to stroke. Elderly, sick, often confused patients find it difficult to remain still for long enough in the MRI scanner to obtain spectra of diagnostic or research use. Although newer imaging techniques based on the robust water signal and rapid, echoplanar imaging such as diffusion-weighted and perfusion-weighted imaging (DWI and PWI, respectively), progressed from research tools to the domain of common clinical use and recognized clinical utility years ago, MRSI remains rarely performed on patients with stroke and even then rarely outside of a research context. The clinical advantage of the measurement of in vivo brain lactate, N-acetyl aspartate and other metabolites that MRSI can provide remains uncertain, a matter largely of theory and conjecture.

In this issue of Stroke, Dani and colleagues report a series of MRSI measurements on a 3-T scanner, performed on patients within 24 hours of hemispheric stroke, who also completed an advanced stroke imaging protocol that included diffusion and perfusion imaging and estimation of any PWI–DWI mismatch. The authors are to be commended for carrying out such an inherently challenging investigation. By limiting the MRSI sequence to a single average, they were able to hold the additional acquisition time to a short 5 minutes (plus volume of interest selection and set-up times), albeit at the inevitable price of a decreased threshold for signal detection from lactate and other metabolites. After discarding a small number of spectra due to technical issues, MRSI voxels were analyzed if they arose from a region with either abnormal perfusion or diffusion MRI, or both, and correlated with the MRI parameters plus the clinical parameters of serum glucose level and time since symptom onset.

The perfusion and diffusion MRI parameters were predictive of the lactate and N-acetyl aspartate metabolite maps, but only in part ($R^2=0.25$ and $R^2=0.26$, respectively). Regions of metabolite mismatch, with relatively preserved N-acetyl aspartate but small signals from increased lactate, were identified that differed from the zones of PWI–DWI mismatch in some cases. There were also voxels within the diffusion lesion (both hypoperfused and reperfused) without measured lactate. Thus, MRSI describes a tissue state in the first hours of stroke that is at least somewhat different from DWI and PWI. The lack of correlation with symptom duration underscores the limitations of using time to predict tissue state (and by inference, likelihood of response to intervention), and in this regard, MRSI and diffusion–perfusion MRI are in agreement. The correlation with glucose level is also interesting, although cause and effect are more difficult to sort out. The authors rightly note that hyperglycemia at the time of a stroke is correlated with more severe injury and worse outcome, but increased brain lactate in hyperglycemic patients may also simply reflect presence of a greater amount of glucose substrate that the brain can metabolize anaerobically.4

There are important limitations of the study, many of which the authors acknowledge. The study was a retrospective analysis of a series of cases in which MRSI data were obtained at the discretion of the treating clinicians, creating possible patient selection biases that are difficult to assess or disentangle. Given the median postonset study time of 4.5 hours, half of these acute patients underwent MR examination outside the window in which intravenous thrombolysis has been shown to be efficacious. Perhaps most importantly, there is a tautology inherent in selecting voxels of interest based on their location largely or fully within regions of abnormal DWI and/or PWI, and then finding that some of the MRSI metabolite levels correlate with DWI- and PWI-derived parameters. However, this criticism is mitigated by the fact that Dani et al really did not have another viable choice, because reference to another, external standard such as positron emission tomography imaging is impractical in this acute clinical setting.
Does MR spectroscopy add enough value, enough significant clinical information, to justify the additional examination time and effort (and in some cases, additional patient distress) required to add it to the MR protocol for patients with acute stroke? Dani et al demonstrated that diffusion and perfusion MRI only partially predicted the levels of lactate and N-acetyl aspartate, suggesting that spectroscopy may in fact provide some new information and perhaps a new way of identifying at-risk tissues. A definitive answer will require additional data from future studies. Furthermore, even the comparator MRI measures of mismatch are not a true “gold standard,” because the acute perfusion deficits often overestimate the zone of clinically significant ischemia, and acute lesions on diffusion-weighted images may regress or disappear in time. The true value of MRSI in stroke will not be manifest until there are therapies whose use depends on the MRSI profile—a tall order, because many would argue that even PWI–DWI mismatch does not yet meet this test. MR spectroscopy end points have been used in clinical trials of acute stroke therapies, but only rarely, and perhaps most justifiably when the intervention was hypothesized directly to alter levels of one of the measured metabolites such as lactate. To date, neither clinical nor MRI measures alone have predicted benefit from neuroprotective agents in human stroke. Of course, the fault may lie with the agents themselves or with their inability to reach ischemic brain, but because MRI and clinical assessment have not yet identified patients amenable to novel therapies, perhaps MRSI deserves a second chance.

References


**Key Words:** diffusion magnetic resonance imaging ◼ echoplanar imaging ◼ magnetic resonance spectroscopy ◼ neuroimaging ◼ stroke

Disclosures

None.