Editorial for "Phase I Randomized Trial of ^{17}O-Labeled Water: Safety and Feasibility Study of Indirect Proton MRI for the Evaluation of Cerebral Water Dynamics": old concepts, new applications

On the long-term, fundamental and applied sciences cannot be dissociated. MRI, for instance, uses many concepts or ideas dating for the early days of NMR, years before Lauterbur and Mansfield had the brilliant idea of using magnetic field gradients to localize the MR signal of body hydrogen protons. The sequences developed in the 1950s to measure relaxation rates in liquids, as the spin echo sequence,[1] are at the origin of most of the imaging sequences used nowadays in hospitals. Similarly, water proton relaxation induced by the presence of paramagnetic ions, among which Gd^{3+}, has been studied[2] experimentally and theoretically modeled 30 years before the first use of a gadolinium-based contrast agent in 1988.

In the 1960s, Zeev Luz and Saul Meiboom published a series of papers studying the kinetics of proton exchange in aqueous solutions of different buffers,[3] ingeniously using the water proton relaxation caused by the coupling with the spin of oxygen in ^{17}O-enriched water. At that time, they certainly did not imagine that their idea could be used to measure the cerebral blood flow with a noninvasive imaging technique based on NMR.

If the most abundant isotope of oxygen (^{16}O) is NMR silent, the ^{17}O isotope—whose abundancy is only 0.037%—has a spin of 5/2. In a $H_2{}^{17}O$ water molecule, the scalar coupling between the hydrogen spin 1/2 and the ^{17}O spin 5/2 causes a faster proton relaxation than in $H_2{}^{16}O$, where relaxation is only due to the dipolar coupling between hydrogen spins either from the same molecule or from the two neighboring molecules. In solutions containing both $H_2{}^{17}O$ and $H_2{}^{16}O$, this "^{17}O relaxation effect" is transmitted to all the water protons of the sample through fast proton exchange, and the global T_2 of the sample logically increases with the $[H_2{}^{17}O]/[H_2{}^{16}O]$ fraction. This has been shown in water, but also in gelatin phantoms, in protein solutions, and in cerebrospinal fluid.[4,5] This means that the $H_2{}^{17}O$ fraction can be evaluated by a simple measurement of the water proton transverse relaxation rate $1/T_2$: it is an indirect ^{17}O detection through proton relaxation. The direct NMR detection of ^{17}O nuclei is also feasible, even if the signal-to-noise ratio is low, but it implies the use of specific hardware tuned at the ^{17}O Larmor frequency, which makes it hard to implement in the clinic.

In vivo, after injection of ^{17}O-enriched water, the cerebral blood flow (CBF) can thus in principle be followed by proton MRI thanks to the change in T_2-weighted signal observed in the brain, as first shown in animals[6–8] and then in humans.[9] It necessitates the use of fast T_2-weighted sequences, as steady-state free precession (SSFP), to reduce the scan time and increase the temporal resolution, which is mandatory for kinetic studies. In this issue of *JMRI*, Harada and coworkers report the results of the first phase 1 randomized trial, on 12 volunteers, of ^{17}O-labeled water for the evaluation of cerebral water dynamics.[10] They show the absence of adverse effects after injection of ^{17}O-labeled water and the urine and blood tests performed at different time intervals remained normal. A biological half-life $T_{1/2}$ of 160 h was determined for ^{17}O-labeled water thanks to the analysis of blood samples with isotope ratio mass spectrometry. The brain images were obtained with a 3D-FLAIR sequence instead of SSFP in order to suppress the high signal of cerebrospinal fluid, which may "hide" changes in the brain signal caused by the presence of $H_2{}^{17}O$. However, this was done at the cost of spatial resolution, in order to keep a suited temporal resolution of about 10 s. The results of this study must be confirmed with a larger number of subjects and the imaging sequence must be optimized to achieve better spatial and temporal resolution. However, the work of Harada et al shows that indirect proton imaging of ^{17}O for the study of cerebral blood flow in humans is safe and deserves further development for benchmarking this approach against classical CBF evaluation using dynamic susceptibility (DSC)-MRI or arterial spin labeling (ASL)-MRI. If only Luz and Meiboom knew.

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Technical Efficacy: Stage 1