Comparison of chemical exchange saturation transfer (CEST) and T1p MRI for measurement of proton chemical exchange between metabolites and water at 7T

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Introduction: Chemical exchange between labile protons of proteins and water protons can make Magnetic Resonance Imaging (MRI) sensitive to information about the concentrations of endogenous proteins and their environments. Chemical Exchange Saturation Transfer (CEST), a technique which uses the attenuation of bulk water magnetization through magnetization exchange with saturated labile protons, has become a popular method for measurement of metabolites with exchangeable protons1-3. While CEST has been well established over the past decade as a method for measuring proton exchange, spin-lattice relaxation in the rotating frame (T1p) is another technique which is sensitive to proton exchange but has yet to be thoroughly investigated4-8. In this article, we compare the sensitivity of CEST and T1p MRI for imaging proton exchange and showed that at 7T, T1pMRI has a higher sensitivity.

Theory: In order to remove the direct water saturation which plagues CEST imaging, CEST proton transfer ratio (PTR) is thus quantified by

\[
\text{CEST } \% \text{ Contrast} = \frac{M_{ss}^{(-\text{offset})} - M_{ss}^{(+\text{offset})}}{M_0} \times 100\% \tag{1}
\]

where [Mss (+offset)]/[Mss (-offset)] are the magnetization signal at the positive (labile proton saturation site) and negative (no labile proton saturation) offsets with respect to water respectively and M0 is the control magnetization signal without selective irradiation8. For T1p imaging, applying a low amplitude spin-lock (B1) results in relaxation highly dependent on chemical exchange. However, when a high amplitude spin-lock is applied, the chemical exchange effects are minimized. Thus by subtracting T1p maps acquired at high(T1p_low) and low spin-lock(T1p_low) amplitudes, the effect of the chemical exchange can be isolated. We thus define the effect due T1p PTR as

\[
\text{T1p } \% \text{ Contrast} = \frac{T1p_{\text{High}B1} - T1p_{\text{Low}B1}}{T1p_{\text{High}B1}} \times 100\% \tag{2}
\]

Method: A sample of Lysine, which has an amino group (-NH2) capable of exchanging protons with bulkwater, was prepared at a concentration of 20 mM in deionized water at a pH of 6.0. Lysine –NH2 has a resonance frequency of 3 ppm relative to water resonance. Imaging experiments were performed on a Siemens 7.0T whole body MRI scanner using a custom built radiofrequency coil. Imaging was performed using a CEST T1p magnetization preparation pulse followed by a turbo spin echo (TSE) readout. CEST magnetization preparation utilized a low irradiation pulse. CEST Images were acquired with a 3000 ms saturation pulse at +3 ppm-3ppm at various B1 in order to determine a maximum CEST effect. The T1p magnetization preparation pulse consisted of a 90° RF pulse which tips the longitudinal magnetization into the transverse plane followed by two spin-lock pulses of equal length and amplitude. The spin-lock pulses are phase alternating in order to refocus the effect of an inhomogeneous B1 field. T1p maps where constructed for high (2000 Hz) and low (100 Hz) spin-lock amplitudes from images acquired at various spin-lock lengths.

Results and Discussion: Figure 1 shows T1p (a,b) images and CEST (c,d) maps of the lysine sample only with (a,c) and without (b,d) the presence of chemical exchange. As seen from the figures, both techniques and sensitivity were stronger with CEST imaging shows higher sensitivity. This is further highlighted in figure 2 which shows the % change due to chemical exchange for each respective method computed using the images in Figure 1 and equations (1) and (2). Images in figure 2 also show the de-ionized water, in which the NMR tubes containing the lysine samples were held. CEST shows an average change of 37.2 % while T1p shows a change of 67.0%. Equally important to % change due to chemical exchange, both images show that there were minimal differences in the water between images taken to include and exclude the presence of chemical exchange. Small differences can be due to noise and magnetic field inhomogeneities. However, the lack of difference seen in the water proves that differences seen in the lysine samples are due to chemical exchange and not to intrinsic properties of the techniques themselves.

Imaging at higher static magnetic fields is very important for imaging of proton exchange in both of these methods. For CEST imaging this higher sensitivity is explained by a larger chemical shift difference between solute and water which decreases the effects of direct saturation of water. Additionally, the T1 relaxation rate of T1p imaging decreases as field strength increases. This prolongs the storage of transferred saturation in the water pool thus resulting in an increase in PTR. For T1p imaging, relaxation rates scale as the square of the difference in proton chemical shift. As this difference increases linearly with magnetic field, T1p chemical exchange effects vary quadratically with the static magnetic field.

Conclusion: In this study we demonstrated that while both CEST and T1p imaging can be used to image proton exchange between solutes with exchangeable protons and water, T1p imaging is more sensitive to these processes. Specifically, in the lysine sample studied here, the T1p method has roughly a factor of two higher sensitivity compared to CEST. Further, this sensitivity differences are expected to depend on the chemical exchange rates of the exchangeable protons. Further studies are in progress to model these effects and determine the optimal experimental conditions applicable to each method.


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