The CEST effect of guanidine and hydroxyl protons can be used as a positive contrast in ischemia

Tao Jin1 and Seong-Gi Kim1

1Department of Radiology, University of Pittsburgh, Pittsburgh, PA, United States

Target Audience Researchers interested in the chemical exchange saturation transfer (CEST) technique and MR imaging of stroke.

Purpose CEST imaging based on the endogenous amide-proton transfer (APT) effect has shown great potential in stroke studies. However, the APT contrast in stroke is negative which decreases at the lesion region. When the conventional symmetry analysis is applied to obtain APT-weighted images, its sensitivity in detecting the ischemic lesion is limited by large negative background interference from the asymmetry of magnetization transfer contrast and the nuclear Overhauser effect. Moreover, the amide water proton exchange rate and the magnitude of APT effect decrease with pH exponentially; therefore, its sensitivity quickly diminishes at lower pH (e.g., ≤6.4), which makes it difficult to differentiate mild versus severe tissue acidosis. Alternatively, the chemical exchange (CE) effect of endogenous guanidine and hydroxyl protons may be exploited for pH-selective imaging. Because guanidine and hydroxyl protons exchange with water at much faster rate than amide protons, a positive contrast may be detected by judicious selection of B1, the power of off-resonance irradiation pulse. In this preliminary study, we investigated the CEST effects of guanidine and hydroxyl protons and their potential application in stroke studies.

Materials and Methods Simulation $M_{\text{TR}_{\text{sym}}}$ was simulated as a function of labile water exchange rate ($k$). Three pool exchanges between free water protons, labile protons, and bound water protons were simulated by modified Bloch Equations where the lineshape of bound water was modeled by a super-Lorentzian function. We assumed a bound water proton fraction of 0.05, a labile proton fraction of 0.0005, a chemical shift between labile water and proton of 2 ppm, and the magnetization transfer rate between bound water and free water of 50 s$^{-1}$. The $T_1$ ($T_2$) of water, labile proton, and bound water protons were assumed to be 2 s (50 ms), 2 s (50 ms), and 2 s (13 μs), respectively.

Experiments All experiments were performed at 9.4 T. Phantom experiment: 15 mg/ml protamine was dissolved in phosphate buffered saline (PBS) and titrated to pH values of 6.1, 6.4, 6.7, and 7.0, and 0.15 mM MnCl$_2$ was added to each sample to shorten the $T_2$ values. Z-spectra of phantoms were measured at 37°C with a 0.5 μT and 4 s continuous wave pulse. In vivo experiments: Five Sprague-Dawley rats underwent permanent middle cerebral artery occlusion (MCAO). Z-spectra were measured after 5 hours of ischemia onset. Off-resonance irradiation was applied by a 0.8 μT and 4-s saturation pulse, and a frequency offset range from 12 ppm to -12 ppm. Apparent diffusion coefficient (ADC) maps were also measured to identify the ischemic regions. For quantitative data analysis, Z-spectra were obtained from the regions of interest (ROI) selected at the contralateral and ipsilateral areas, based on the ADC map.

Results and discussions At normal physiological conditions, guanidine and hydroxyl protons have a chemical shift of ~1-2 ppm relative to water, and exchange with water protons at rates of around 1000 s$^{-1}$. Compared to amide, one distinct disadvantage of utilizing the guanidine and hydroxyl groups in CEST study is their Larmor frequencies to be of ~1-2 ppm relative to water, and exchange with water protons at rates of around 1000 s$^{-1}$. The guanidine exchange rate at lower pH is farther from the tuned rate (see Fig. 1).

The CEST effect of guanidine and hydroxyl protons can be used as a positive contrast in ischemia. Note that due to the close proximity of guanidine and hydroxyl protons to the water frequency, the amide water proton exchange rate and the magnitude of APT effect decrease with pH exponentially; therefore, its sensitivity quickly diminishes at lower pH (e.g., ≤6.4), which makes it difficult to differentiate mild versus severe tissue acidosis. Alternatively, the chemical exchange (CE) effect of endogenous guanidine and hydroxyl protons may be exploited for pH-selective imaging. Because guanidine and hydroxyl protons exchange with water at much faster rate than amide protons, a positive contrast may be detected by judicious selection of B1, the power of off-resonance irradiation pulse. In this preliminary study, we investigated the CEST effects of guanidine and hydroxyl protons and their potential application in stroke studies.

References