Oxidative Stress Sensitive Magnetization Transfer

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Target audience: Scientists or clinicians who are interested in oxidative stress, magnetization transfer through chemical exchange saturation transfer (CEST) and dipolar-dipolar interaction (Nuclear Overhauser Enhancement, NOE).

Purpose: Reactive oxygen species (ROS) including hydrogen peroxide (H_2O_2) formed *in vivo* are powerful oxidizing agents. Increased formation of ROS may lead to oxidative damage that has been linked to pathologic changes such as neurodegenerative diseases[1]. It has been demonstrate that tumor redox state heterogeneity revealed by the optical redox scanning of *ex vivo* tissues is associated with tumor aggressiveness[2]. Our recent work showed that the tissue redox state measured by optical scanning was proportional to the endogenous Chemical Exchange Saturation Transfer (CEST) contrast in MRI[3,4]. Since magnetization transfer (MT) can occur via CEST and/or dipole-dipole interactions (Nuclear Overhauser Enhancement or NOE), this study aims to investigate the sensitivity of MT in the broad definition to oxidative stress through controlled *ex vivo* studies and to test the feasibility of utilizing MT as a non-invasive and endogenous imaging biomarker for tissue oxidative stress.

Methods: Egg white tissues (n=3) were treated with H_2O_2 at room temperature by adding various concentrations of H_2O_2 (0.25, 0.1, 0.05, 0.025, and 0 v/v%). Samples in 10 ml NMR tubes were scanned at a Varian 9.4-T horizontal MRI scanner before and 1 hour after the H_2O_2 incubation. CEST z-spectra were collected using a custom sequence[5] with a frequency selective rectangle saturation pulse (B_1=50 Hz, 3 s) followed by Fast Low-Angle Shot (FLASH) readout. Other parameters includes readout TR/TE = 5/3 ms, shot TR = 10 s, matrix=128x128, slick thickness=1.5mm, and 2 averages. The entire z-spectrum contained 53 saturation offsets from -5 to 5 ppm with an interval of 0.25ppm, ±6, ±8, ±10, ±20, ±50, and ±100ppm. Z-spectra were normalized by the signal at +100 ppm. Magnetization transfer ratio (MTR=100*(1-Mz/M0)) was constructed at 3.5 , -3.25, and 6ppm, the resonances of amide proton transfer (APT), NOE and the conventional broad-band MT(also called the semi-solid MT) respectively[6]. Images for B_1 and B_0 mapping were acquired to correct MTR contrasts for field inhomogeneity[4]. Images for constructing T_1 and T_2 maps were also acquired. pH were monitored from a separate group of egg white tissues for up to 2 hours' H_2O_2 incubation. In addition, *ex vivo* lamb brain tissues (n=3) were incubated with 0.02 v/v% H_2O_2 and scanned pre and 1 hour post incubation at room temperature using the same imaging protocols. Averaged Z-spectra form white and gray matters were derived from 3 ROIs based on T_2-weighted anatomical images. Similar to the *in vivo* situations, treatment with H_2O_2 may produce oxygen. With low H_2O_2 concentration such as 0.025 v/v%, no observable bubbles were seen in tissues after 1 hour of treatment.

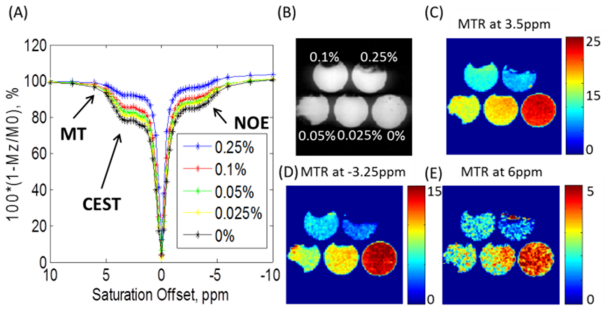

Fig. 1. (A) Z-spectra from treated egg white tissues demonstrating reduced MTR. (B)Anatomical image showing phantoms of egg white treated with different H_2O_2 concentrations. (C)-(E) MTR maps at the resonance frequencies of 3.5 ppm (ATP), -3.25ppm(NOE), and 6ppm (semi-solid MT).

Results: In z-spectra, distinctive reductions in the MTR at the resonances of NOE, CEST and the semi-solid MT were seen from the treated egg white tissues (Fig. 1A). The reductions were dependent on the concentration of H_2O_2 (Fig. 1B and Fig. 2). Remarkable changes in NOE and CEST together with a subtle change in semi-solid MT effect were seen. Similar results were observed in the experiments on lamb brain tissues (Fig. 3 and 4). No notable changes were observed in pH, T_1 and T_2 due to H_2O_2 treatment.

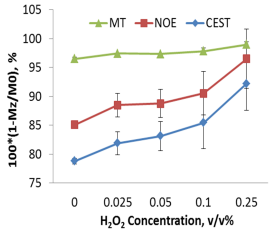

Fig. 2. Averaged MTR contrasts on the resonance of ATP, NOE, and semi-solid MT derived from treated egg white tissues.

Discussion: Induced oxidative stress produces overall changes in z-spectra, demonstrating the sensitivity of magnetization transfer to oxidative stress. This observation is in agreement with our previous study on the correlation of CEST MRI with tissue redox state[4]. The controlled experiments validate the concept that magnetization transfer contrasts through different mechanisms are all modulated by tissue oxidative stress. MT MRI contrasts, once calibrated, may serve as imaging surrogated for tissue oxidative stress.

References: [1] Barnham KJ, et al. Nature Reviews Drug Discovery. 2004;3: 205-214. [2] Li LZ, et al. PNAS. 2009;106:6608-13. [3]Cai K, et al. Adv Exp Med Biol. 2013;765:39-45. [4] Cai K, et al. Mol Imaging Biol. 2014;16:670-9. [5] Cai K, et al. Nat Med. 2012;18:302-6. [6]Cai K, et al. NMR in Biomedicine 2014.

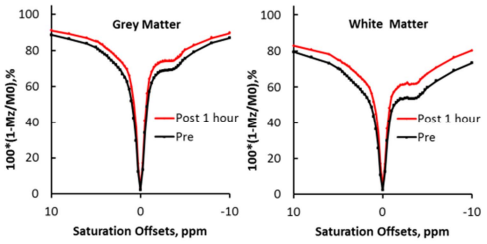

Fig. 3. Z-spectra from pre and 1 hour post H_2O_2 treated lamb brain tissues.

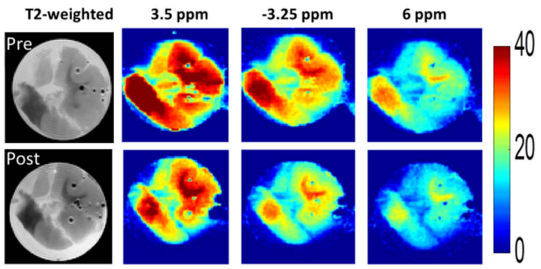

Fig. 4. Representative T2-weighted and MTR maps of pre- and post-treated lamb brain tissues.