Chemical Exchange Contrast with Off-Resonance Spin Locking

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Introduction: 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 endogenous metabolites with exchangeable protons[1]. One of the key concerns of current CEST techniques is the direct saturation of water protons or spillover effects which lead to a decreased signal to noise ratio (SNR) and CEST contrast[2]. This is particularly concerning when imaging metabolites with proton exchange sites close to water such as hydroxyl protons or those with faster exchange rates that require larger saturation amplitudes. Shaped saturation pulses such as Hanning windowed and Gaussian pulses have addressed these concerns and decreased spillover but at the cost of less efficient saturation of exchange protons. In order to address these concerns, we propose utilizing an off-resonance spin-lock (SL) pulse for generating the exchange mediated contrast. This technique will decrease direct water saturation and increase the saturation efficiency over shaped saturation pulses, particularly when saturating with high amplitudes or at exchange sites close to water.

Theory: In CEST, an off-resonance saturation pulse with amplitude ω_1, is applied at the resonance frequency of the labile protons ($\Delta\omega$). This results in the saturation of labile protons but also acts on water protons with $B_{1,eff} = \sqrt{\omega_1^2 + \Delta\omega^2}/\gamma$. This leads to the direct saturation of the water protons. To remove the frequency dependant direct saturation effects, the CEST asymmetry ratio is defined as

$$CEST_{asym}\ or\ SL_{asym}\ (\Delta\omega) = \frac{M_{sat}(-\Delta\omega) - M_{sat}(+\Delta\omega)}{M_O} \qquad [1]$$

However, while the effects of direct water saturation can be removed using the equation above, these spillover effects still attenuate the $CEST_{asym}$. For off-resonance SL, the water magnetization is first flipped to the Y-Z plane by an angle θ and then spin-locked by $B_{1,eff}$ before being flipped back to the z axis for imaging[3]. During the SL time, the water magnetization is locked at angle $\theta = \tan^{-1}(\omega_1/\Delta\omega)$. The SL pulse acts not only as locking pulse on water protons but also as a saturation pulse on labile protons. Like with CEST, we can define the SL ratio, $SL_{asym} = CEST_{asym}$, as the effects of SL pulse on water protons will be symmetric on both sides of the water resonance and can be removed using eq. (1). Jin et al. showed that the SL_{asym} and $CEST_{asym}$ match very well for larger frequency saturation offsets where θ is small[4]. However, for larger amplitude saturation pulses or labile proton exchange sites close to the water resonance where $B_{1,eff}$ and θ are larger, the SL_{asym} will be greater than the $CEST_{asym}$ due to smaller spillover effects. Shaped saturation pulses are used for CEST to reduce the spillover effects and remove artifacts associated with rectangular pulses. In contrast, spin locking flips the water magnetization down to the effective field and then applies a rectangular off resonance locking pulse which allows for more efficient saturation of labile protons than shaped pulses of equivalent root mean squared (rms) $B_{1,rms}$ without additional artifacts.

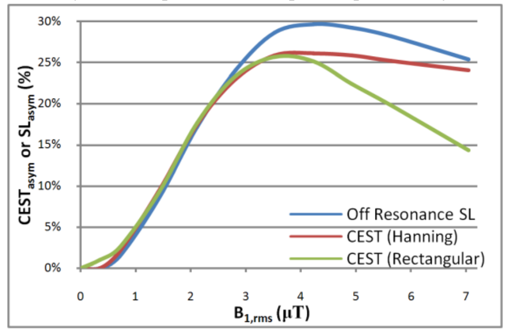

Figure 1: $CEST_{asym}/SL_{asym}$ as a function $B_{1,rms}$ for 5% CS phantoms with rectangular and Hanning windowed CEST or off resonance spin locking pulses

Methods: All imaging experiments were performed on a 7T whole body scanner (Siemens Medical Systems, Erlangen, Germany). The CEST saturation pulse utilized a pulsed Hanning windowed off-resonance saturation pulse while the off resonance SL pulse is described above and used rectangular pulses for excitation and pulsed spin locking. A pulsed rectangular saturation pulse was also used for CEST in phantom studies for comparison. All sequences used a segmented RF spoiled gradient echo (GRE) readout. For phantom experiments, Chondroitin sulfate (CS), which has hydroxyl groups (-OH) capable of exchanging protons with bulk water, was used for imaging[5]. 5% CS by weight was dissolved in phosphate buffered saline, titrated to physiological pH and imaged using the three imaging sequence mentioned above. The $B_{1,rms}$ for each pulse was varied from 0 to 7 μT (300 Hz) for a constant saturation time (t_{sat}) or SL time (TSL) of 1 second. The $CEST_{asym}$ and SL_{asym} were calculated from images using eq. (1). For *in vivo* imaging, glucosaminoglycans (GAG) in the patellar cartilage of a healthy human subject were imaged with the Hanning windowed CEST pulse and the off resonance SL pulse mentioned above. GAG has 3 hydroxyl groups (-OH) which are capable of exchanging with water protons. $B_{1,rms}$ = 2.35 μT and t_{sat}/TSL = 500 ms. Again, $CEST_{asym}$ and SL_{asym} maps were computed using eq. (1) and were similarly corrected for B_0 and B_1 inhomogeneities.

Results and Discussion: Figure 1 shows the relationship between the $CEST_{asym}/SL_{asym}$ of the three different pulse sequences as a function of $B_{1,rms}$ for 5% CS phantoms. When the $B_{1,rms}$ is small, the $CEST_{asym}/SL_{asym}$ of all three methods is similar. At low B_1, the $B_{1,eff}$ experienced by water protons is small, which results in minimal direct water saturation. Thus, increases in saturation power result in linear increases in $CEST_{asym}/SL_{asym}$ due mainly to an increase in the saturation of labile protons. As the amplitude of the B_1 irradiation pulse is further increased, so are the direct saturation effects. When the spillover effects increase, the asymmetry curves as a function of B_1 lose linearity. As shown in figure 1, this occurs for $CEST_{asym}$ curves at a lower $B_{1,rms}$ than for the off resonance SL_{asym} curve. The maximum $CEST_{asym}/SL_{asym}$ occurs when labile proton saturation is close to its maximum and spillover effects are minimized. Again, this maximum occurs at a higher $CEST_{asym}/SL_{asym}$ for the off resonance SL sequence because there is less direct water saturation when saturation is close to maximum. Following this maximum, increases in B_1 result in increases in direct water saturation with minimal increases in labile proton saturation and thus result in a decrease in the $CEST_{asym}/SL_{asym}$. The rate of this decrease is dependent on the shape and thus bandwidth of the pulse for which the shaped Hanning windowed saturation pulse has a more optimal profile. Figure 2 shows CEST and SL asymmetry maps of a human patellar cartilage at 7T. Both methods have similar distributions of chemical exchange contrast. This demonstrates that both sequences are imaging the same exchangeable protons and have a similar dependence on exchange rate. However, the average SL_{asym} (6.9%) observed in the cartilage was higher than the $CEST_{asym}$ (6.0%). The SNR of the two methods were similar and thus the 15% increase in asymmetry values shows that the SL method has increased sensitivity to chemical exchange. This will be particularly applicable to imaging faster exchange species which require higher saturation amplitudes to optimize chemical exchange contrast. Another application is chemical exchange imaging at lower magnetic fields where the chemical shift of exchangeable protons is closer to water and thus direct water saturation effects are magnified.

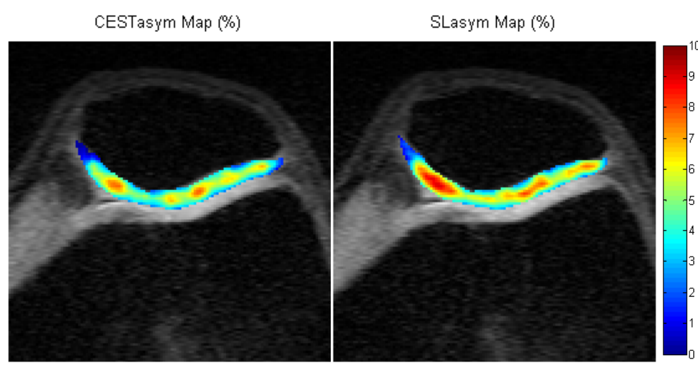

Figure 2: $CEST_{asym}/SL_{asym}$ Maps of human patellar cartilage at 7T. (Corrected for B_1 & B_0)

Conclusion: In this work we discussed the use of an off-resonance SL pulse for generating the exchange mediated contrast in order to decrease direct water saturation and thus increase chemical exchange asymmetry at higher saturation amplitudes. We showed the feasibility of using the SL method *in vivo* in the human patellar cartilage and showed that the SL method was 15% more sensitive to chemical exchange than conventional CEST.

References: [1] Wolff et al. *J Magn Reson*. 86(1990): 164–169, [2] Sun et al. *J Magn Reson*. 175(2005): 193-200 [3] Santyr et al. *Magn Reson Med*. 32(1994): 43-51 [4] Jin et al. *Magn Reson Med*. 65(2011): 1448-1460 [5] Ling et al. *Proc Natl Acad Sci*. 105(2008):2266-2270