Improved measurement of labile proton concentration-weighted chemical exchange rate (kws) with experimental factor-compensated chemical exchange saturation transfer (CEST) MRI

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Introduction CEST MRI provides an exchange-dependent contrast mechanism that enables measuring low concentration CEST agents and microenvironment properties, and remains promising for a host of in vivo applications[1-7]. However, CEST MRI contrast is complex, depending on not only the labile proton concentration and exchange rate, but also on experimental parameters such as field strength and RF irradiation power. There is a demonstrable need to develop quantitative CEST MRI for improved mechanistic understanding of the underlying CEST system. The CEST MRI contrast can be described as a multiplication of the simplistic CEST contrast and an experimental factor that includes the labeling coefficient and spillover factor[8,9]. The labeling coefficient quantifies the saturation efficiency of the exchangeable protons, while the spillover factor calculates the direct RF saturation of the bulk water signal, which competes with the CEST effect. We postulated that the reverse chemical exchange rate (k_{ws}) could be derived from CEST MRI with reasonable estimation of the experimental factor.

Materials and Methods Phantom: Creatine solution phantom was added to gadolinium-doped phosphate buffered solution (PBS) at concentrations of 20, 40, 60, 80 and 100 mM; pH was titrated to 6.75 (within ± 0.01). MRI: Single-slice, single-shot echo planar imaging (EPI) images were obtained at 4.7 T. For the CEST MRI, 3-point CEST imaging was performed with continuous wave (CW) RF irradiation applied at ±1.875 ppm, in addition to a control scan. The RF power was varied from 1, 1.5, 2, 2.5, 3, 3.5 and 4 μT. In addition, the Z-spectrum was acquired with RF irradiation from -3 to 3 ppm, per 0.125 ppm (B_1=2 μT). T_1 (TR/TE =12,000/28 ms, NA=2) and T_2 (TR=12,000 ms, NA=2) were obtained using an inversion recovery and spin echo sequences, respectively.

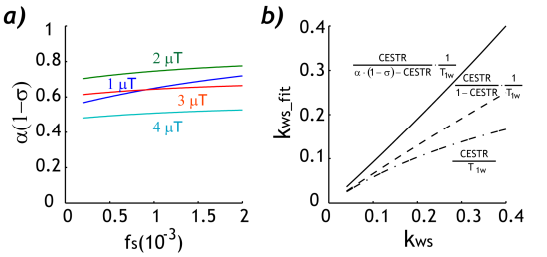

Fig. 1, Experimental factor (η) as a function of CEST agent concentration (fs). a) η remains nearly constant with fs when intermediate RF power level is used. b) Experimental factor-compensated k_{ws} is significantly improved from simplifies solutions.

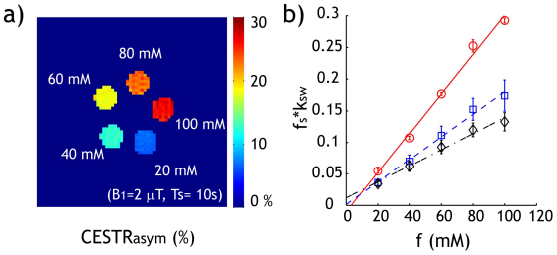

Fig. 2, Quantitative CEST MRI. a) CEST contrast is sensitive to agent concentration. b) The accuracy of k_{ws} estimation improves using the proposed algorithm, in good agreement with simulation.

Results and Discussion Simulation shows that the labeling coefficient increases slightly with RF power, which remains relatively constant with respect to CEST agent concentration for RF power above 2 μT. The RF spillover factor decreases with RF power. Importantly, the spillover factor shows relatively little change as a function of CEST agent concentration while the experimental factor increases only slightly, at 0.65 ± 0.04, 0.75 ± 0.02, 0.64 ± 0.01 and 0.51 ± 0.01 for B_1 fields of 1, 2, 3 and 4 μT, respectively. Therefore, the experimental factor remains rather constant (within 2%), for B_1 field stronger than 2 μT (Fig. 1a). Fig. 1b compares k_{ws} estimated by using the first-order approximation of the simplistic solution, the simplistic solution and the proposed experimental factor-corrected analysis. The CEST labile proton concentration with respect to bulk water protons was varied from 1:5000 to 1:500 for a constant exchange rate of 200 s^{-1}. The first-order approximation of the simplistic solution appears to plateau at higher concentration (dash-dotted line). The solution can be improved by the simplistic solution (i.e., CESTR/(1-CESTR)/T_1), which, however, still significantly underestimated the reverse exchange rate (gray dashed line). The experimental factor can be reasonably estimated, assuming a median CEST concentration (1:909) and exchange rate of 200 s^{-1}. Indeed, the proposed solution improved the calculation (solid line). This suggests that by correcting for the experimental factor, the accuracy of the quantitative CEST MRI can be significantly improved.

Fig. 2a shows that the CESTR increases with serial CEST agent concentration. The CEST asymmetry spectra were numerically fitted, using the Bloch-McConnell equation, from 1 to 3 ppm. The exchange rate was determined to be 222 s^{-1}, and the labile proton concentration with respect to the bulk water pool was 1:3999, 1:1999, 1:1333, 1:1000 and 1:800 for 20, 40, 60, 80 and 100 mM Creatine solution. Therefore, we have K_{ws}=0.0028 [C], where [C] is the Creatine concentration in mM. Fig. 2 b shows the calculated reverse exchange rate as a function of Creatine concentration. For the proposed experimental factor-corrected algorithm, the experimental factor was estimated assuming that k_{sw} was 200 s^{-1} at labile proton concentration of 1:1000. Moreover, we assumed T_1 and T_2 to be 1.76 and 1.18 s, respectively, from the extrapolated T_1 and T_2 measurements. We repeated the calculation for RF powers of 2, 2.5, 3, 3.5 and 4 μT, as suggested by Fig. 1. The results can be described by linear regression, where K_{ws}=0.0013 [C] + 0.0119, K_{ws}=0.0018 [C] + 0.0015 and K_{ws}=0.0031 [C] - 0.0097, for the first-order approximation of the simplistic solution (diamond), the simplistic solution (square), and the proposed solution (circle), respectively. The proposed solution is approximately equal to that obtained from the Bloch-McConnell numerical fitting (i.e. K_{ws}=0.0028 [C]), significantly improved from the results of the conventional solutions. In summary, the proposed solution provides more accurate measurement than conventional CEST-weighted MRI contrast, which will thus further aid the development of quantitative CEST imaging.

References 1) Ward et al. JMR 2000;143:79-87. 2) Zhang JACS 2005;127:17572-3. 3) Gilad et al. Nat Biotecholo 2007; 25:217-9. 4) Zhou et al. Nat Med. 2011;17:130-4. 5) Sun et al. JCBFM 2011;31:1743-1750. 6) Shah et al. MRM 2011;65:432-7. 7) Longo et al MRM 2011;65:202-11. 8) McMahon et al MRM 2006;55:836-47. 9) Sun et al. JMR 2005;175:193-200.