An Investigation of Optimizing and Translating Pulsed-Chemical Exchange Saturation Transfer (CEST) Imaging to a 3 T Clinical Scanner

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INTRODUCTION CEST imaging provides a sensitivity enhancement mechanism that enables MRI, which usually detects bulk water signal only, sensitive to certain labile metabolites and their byproducts (1-2). In particular, the chemical exchange between bulk water and endogenous amide protons is pH-dependent, which has been dubbed amide proton transfer (APT) imaging (3). As ischemic tissue pH decreases subsequent to abnormal glucose/oxygen metabolism, pH-weighted APT imaging may serve as a surrogate metabolic imaging marker, in complementary to perfusion and diffusion MRI for delineation of ischemic tissue (4). For pre-clinical CEST imaging, long continuous-wave (CW) RF irradiation is applied so that the steady state CEST contrast can be reached. On clinical scanners, however, specific absorption rate (SAR) limit and hardware design preclude the use of CW irradiation, and instead require an irradiation scheme of repetitive RF pulses (pulsed-CEST imaging). In this work, CW- and pulsed-CEST MRI were systematically compared using a tissue-like pH phantom. The results showed that the maximally obtainable pulsed-CEST contrast is about 95% of CW-CEST contrast, and their optimal RF irradiation powers are equal. Moreover, the pulsed-APT imaging sequence was translated to a 3 Tesla scanner and obtained pilot scans from brain-size tissue like pH phantom and control human volunteers, warranting future APT MRI of stroke patients to fully elucidate its diagnostic value.

MATERIALS AND METHODS The tissue-like triple-pH gel phantom contains creatine (50 mM) and low gelling point Agarose (3%) mixture, with pH titrated to 5.2, 6.0 and 6.4, respectively, and imaged at 9.4 T. The RF irradiation power was varied from 0.3 to 3.9 μT in order to compare the optimal RF power and maximal CEST contrast. Additional creatine-gel mixture was prepared, with their pH titrated to 5.2, 5.9 and 6.5. Another tube of creatine solution was titrated to pH of 5.8. The four Falcon tubes were bound together and transferred into a brain-size container doped with 1 mM $CuSO_5 \cdot 5H_2O$, and imaged at a 3 Tesla Siemens scanner. Four normal volunteers (mean age=33±5 years, M=3, F=1) were enrolled in the scan, approved by Partners HealthCare research review board with signed consent forms obtained prior to MRI.

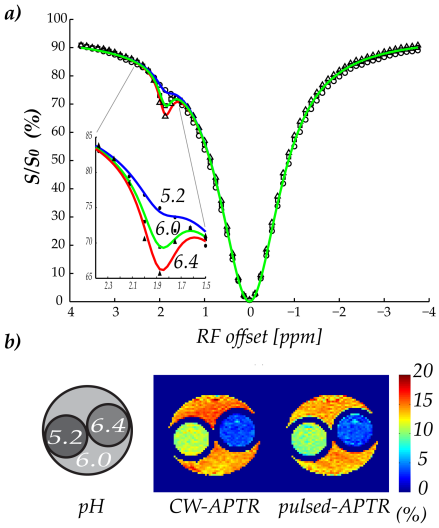

Fig. 1 a) Z-spectra from tissue-like triple-pH phantom obtained at 9.4 T. It shows pH-specific CEST contrast at 1.9 ppm. b) The APTR map obtained CW- and pulsed-APT imaging show nearly identical pH contrast.

RESULTS Fig. 1a shows three z-spectra acquired from the triple-pH phantom, showing pH-specific CEST contrast at the labile amine protons frequency (1.9 ppm). The z-spectra were concurrently fit using a 3-pool exchange model modified from that of Woessner et al. (5), with blue, green and red lines representing the fitting for pH of 5.2, 6.0 and 6.4, respectively. The corresponding chemical exchange rate was found to be 25 s^{-1}, 57 s^{-1} and 85 s^{-1}, respectively. Fig. 1b shows an illustration of the triple-gel phantom and two APTR maps using CW and pulsed RF irradiation at 9.4T (ω_1=0.8 μT). The CESTR obtained with CW irradiation was 3.6 ± 0.9%, 11.0 ± 1.0% and 14.6 ± 1.3% for pH of 5.2, 6.0 and 6.4, respectively. In comparison, the pulsed-CEST imaging contrast was nearly identical, being 3.8 ± 1.3%, 10.0 ± 1.2% and 13.7 ± 1.4%, respectively.

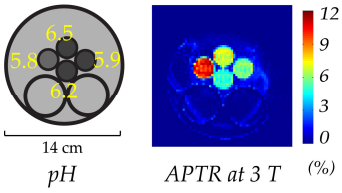

Fig. 2 illustration of a tissue-like quadruple-pH phantom for 3 T, and the corresponding pulsed-APTR image. It clearly depicts pH contrast among different compartments.

Shown in Fig. 2 are an illustration of the quadruple-gel phantom and a pulsed-APTR map at 3 T. The phantom contains four compartments; three are Creatine-Agarose gel mixture titrated at pH of 6.5, 5.9 and 5.3, clockwise from top to bottom, with the leftmost compartment being a 50 mM creatine solution at pH of 5.8. The APTR for gel compartments were found to be 1.5±0.2%, 2.5±0.3% and 3.6 ±0.4% for pH of 5.3, 5.9 and 6.5, respectively. It is interesting to note that the CESTR for creatine solution (pH=5.8) was 10.2±0.7%, even higher than that of creatine gel at pH of 6.3. It is so because the relaxation time (T_1 and T_2) of the creatine solution compartment is significantly longer than those of gel.

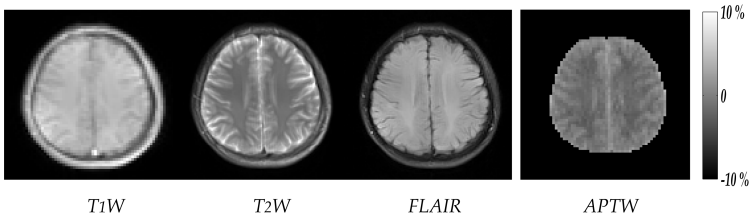

Fig. 3, Representative MRI scan from one normal volunteers, with T1w, T2w, FLAIR and pulsed-APTR image.

Fig. 3 shows T_1-W, T_2-W, FLAIR and APT images from a representative normal volunteer. the APTR of ROI chosen within brain WM was found to be - 4.2±0.2%. In addition, APTR of cerebral spinal fluid (CSF) was found to be -0.15% from a subject whose MRI clearly captured the ventricle body, consistent with the finding of Zhou et al. Given that under optimal experimental condition, the APTR contrast between normal and ischemic tissue is 3%, our pilot data strongly suggest that the sensitively of pulsed-APT imaging at 3 T should be sufficient to detect tissue acidosis in clinic.

REFERENCES 1)Zhang S et al, JACS 2003; 2)Aime S et al, MRM 2003; 3)Zhou J et al. Nat Med. 2003. 4)Sun PZ et al. JCBFM 2007. 5) Woessner et al MRM 2005