Characterization of iopamidol chemical exchange saturation transfer (CEST) MRI for ratiometric imaging of pH

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Introduction Chemical exchange saturation transfer (CEST) MRI is capable of imaging labile proton concentration and microenvironment properties such as pH and temperature, and therefore, remains promising for in vivo translation[1,2]. CEST MRI contrast however, is complex; it not only varies with exchange rate and hence, pH, but also the labile proton concentration. Whereas CEST agent concentration can be directly measured in phantoms, its in vivo concentration may be dynamic and heterogeneous, thereby; CEST MRI often provides only pH-weighted information. To address this, ratiometric CEST MRI has been proposed that interrogates CEST effects of multiple distinguishable labile groups so their concentration effect can be normalized, permitting quantitative pH imaging[3]. Specifically, ratiometric CEST MRI of iopamidol has been recently explored for imaging renal pH[4]. Given that iopamidol is a commonly used CT contrast agent, which can pass through damaged blood brain barrier (BBB), it remains extremely important to elucidate its contrast mechanism and pH sensitivity to guide in vivo evaluation of iopamidol pH CEST MRI in cases like tumor and ischemic stroke.

Materials and method Phantom: Two batches of 20 and 40 mM iopamidol (Bracco Imaging, S.p.A., Milan, Italy) phosphate buffered solution (PBS) solution were prepared. Their pH was titrated to 5.5, 6, 6.5, 7, 7.5 and 8, with each transferred into a 5 ml microcentrifuge tube. The iopamidol solution tubes were inserted into two phantom containers, one for each concentration. The phantom container was then filled with Agarose gel (Sigma Aldrich) solution to minimize magnetic field inhomogeneity.
MRI: All experiments were acquired at a 4.7T Bruker Biospec scanner, under room temperature. Image readout was single shot SE EPI, (FOV = 48x48 mm, image matrix = 64 x 64, slice thickness of 3 mm). T_1 was measured using inversion recovery MRI, with seven inversion times (TI) from 100 to 7500 ms, and a recovery time of 12000 ms (TE= 39.5 ms and NA=2). For T_2 MRI, we varied echo time from 50 to 1000 ms (NA=2). For CEST MRI, we obtained Z-spectra from -7 to 7 ppm, with an interval of 0.25 ppm (i.e., ±1400 Hz per 50 Hz at 4.7T). In addition, continuous wave (CW) RF irradiation was applied for 5 s, with its amplitude varied from 1, 1.5, 2, 2.5, 3, 4 to 5 μT (TR/TE =12,000/39.5 ms). Moreover, B1 field was calibrated with a 2 ms block pre-pulse, serially varied from 10° to 180° in 18 steps. Multi-pool CEST MRI was numerically solved in Matlab[5,6].

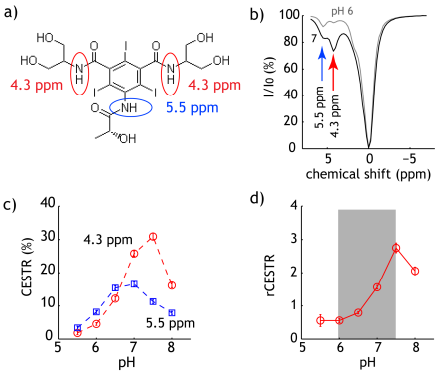

Fig. 1, Iopamidol CEST MRI a) molecular structure of iopamidol. b)Representative Z-spectra of iopamidol at pH 6 and 7. c) CESTR at 4.3 and 5.5 ppm varied with pH differently from each other. d) ratiometric CEST MRI of pH.

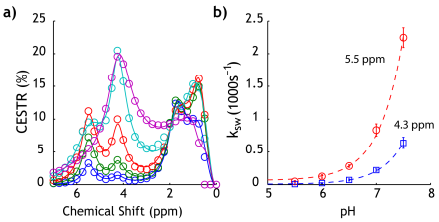

Fig. 2, quantitative analysis of iopamidol CEST MRI. a) Representative fitting of Z-spectra of pH from 5.5 to 7.5. b) Base-catalyzed chemical exchange was found for iopamidol CEST MRI.

Results and Discussion Both iopamidol solution T_1 and T_2 relaxation time decreased with concentration. T_1 was found to be 2.68±0.003 s and 2.5±0.002 s for 20 and 40 mM, respectively. In addition, whereas T_1 showed very little pH dependence, T_2 decreased approximately linearly with pH. This suggests that iopamidol chemical exchange is dominantly based catalyzed.

Fig. 1 a shows the molecular structure of iopamidol, which contains multiple hydroxyl and amide proton groups. Particularly, its amide and 2-hydrooxypropanamido proton groups are at 4.3 and 5.5 ppm, respectively. Two representative Z-spectra of 40 mM iopamidol solution at pH of 6 and 7 are shown in Fig. 1b (B_1= 2 μT), showing CEST attenuation at 4.3 and 5.5 ppm. Whereas both CEST asymmetry ratio (CESTR) increased with pH, CESTR at 5.5 ppm peaked at pH of approximately 7, while CESTR at 4.3 ppm peaked at slightly higher pH of 7.5 (Fig. 1c), enabling ratiometric quantification of pH. The ratiometric CESTR map is shown in Fig. 1d, (i.e., rCESTR = $CESTR_{4.3ppm}/CESTR_{5.5ppm}$), which increased from 0.6±0.1 at pH of 6 to 2.1±0.1 at pH of 7.5, under a representative RF amplitude of 2 μT. As such, our data demonstrated that iopamidol ratiometric CEST MRI is suitable to measure pH from 6 to 7.5. It is important to point out that we also obtained CEST MRI from both 20 mM iopamidol solution, which showed nearly identical ratiometric pH images at 40 mM, despite their large difference in T_1, T_2 and raw CEST contrast at 4.3 and 5.5 ppm (data not shown). This observation demonstrated the advantage of ratiometric CEST MRI in that the concentration and relaxation time difference can be reasonably normalized, simplifying pH calibration.

We numerically solved the exchange properties of labile proton groups with a multi-pool exchange model. Whereas chemical exchange due to hydroxyl group was not apparent in Fig. 1 b, it can be easily appreciated in the CEST asymmetry plot of Fig. 2a, showing two exchange sites at 0.75 ppm and 1.75 ppm, in addition to -NH exchange sites at 4.25 ppm and 5.5 ppm. We concurrently fit CEST asymmetry Z-spectra for pH from 5.5 to 7.5 at each RF power, and found that both-NH groups at 4.3 and 5.5 ppm are indeed base-catalyzed chemical exchange (Fig. 2b). The obtained exchange rate was numerically fit using assuming base-catalyzed exchange ($k(pH) = k_0 + k_b \cdot 10^{pH-pH_w}$). For amide proton at 4.3 ppm, we have k_0= 7s^{-1}, k_b=2*10^7 s^{-1} and pH_w=12, while for 2-hydrooxypropanamido protons at 5.5 ppm, we have k_0= 64 s^{-1}, k_b=3*10^7 s^{-1} and pH_w=11.6. This showed that chemical exchange at 5.5 ppm becomes very fast at higher pH, limiting the dynamic pH range for iopamidol CEST MRI from 6 to 7.5 at field strength of 4.7T or lower.

References 1) Ward et al. JMR 2000;143:79-87. 2) Zhou et al. Nat. Med 2003; 9:1085-90. 3) Ward KM and Balaban RS, MRM 2000; 44:799-02. 4)Longo et al. MRM (in press). 5) Li AX, MRM 2008; 60 (5):1197-06. 6) Sun, JMR 2010; 205 (2):235-41.