Imaging acute ischemic tissue acidosis with quantitative in vivo amide proton transfer (APT) MRI

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Introduction Amide proton transfer (APT) imaging is sensitive to pH with significantly higher spatiotemporal resolution than spectroscopy[1-3]. In vivo APT MRI contrast is often calculated using the magnetization transfer (MT) asymmetry analysis (MTR_{asym}), which is complex due to relaxation and concomitant RF irradiation effects. APT contrast approximately scales with T_1 relaxation time. In addition to the pH-dependent APT contrast, MTR_{asym} is susceptible to slightly asymmetric magnetization transfer effects[4-6]. Moreover, the experimentally obtained CEST MRI contrast strongly varies with RF irradiation power, which can be described using the saturation/labeling coefficient and RF spillover effects[7]. We postulated that tissue pH can be reasonably quantified from pH-weighted APT MRI by taking into account major concomitant RF irradiation effects.

Materials and Methods Animal model: Permanent middle cerebral artery occlusion (MCAO) was induced in adult male Wistar rats (n=12). MRI: All experiments were conducted at 4.7T within 90 min after MCAO. Point-resolved spectroscopy (PRESS) was obtained from a region of interest (ROI) of 3.5 mm^3 (TR/TE=2000/144ms, NA=512) within the DWI lesion. Multi-parametric perfusion, diffusion, pH-weighted APT, T_1 and T_2 MRI (5 slices, 2mm/slice) were obtained (FOV: 25x25mm, matrix: 64x64, bandwidth 200kHz). Specifically, we acquired perfusion (TR/TS/TE=6500/3250/14.8ms, NA=32)[7], APT (NA1/NA2=8/32, TR/TE=6500/14.8ms)[8], diffusion (TR/TE=3250/54ms, b=250 and 1000 s/mm^2, NA=16)[9], T_1 (inversion recovery, TI from 250 to 3000 ms, NA=4) and T_2 (SE MRI, TR/TE1/TE2=3250/30/100 ms, NA=16). We have $MTR_{asym}=\Delta MTR_{asym} + f \cdot k/(R_{1w}+f \cdot k) \cdot \alpha \cdot (1-\sigma)$, where α is labeling coefficient, σ is the RF spillover effect, f and k are the amide proton concentration and exchange rate, and R_{1w} is the bulk tissue water relaxation time.

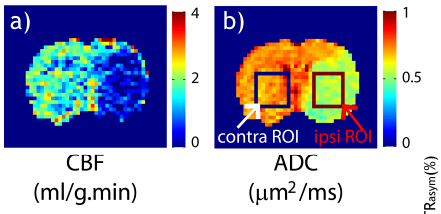

Fig. 1, Perfusion and diffusion MRI lesion of a representative MCAO animal.

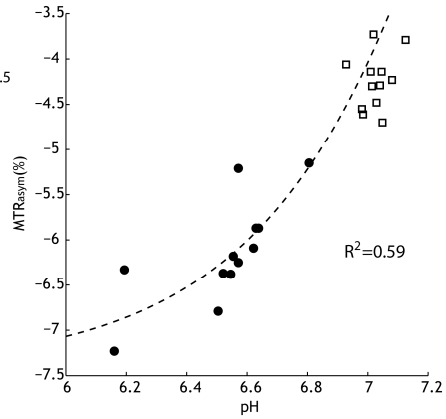

Fig. 2, Numerical fitting of experimentally opbtatined MTR_{asym} as a function of tissue pH, estimated from quantitative lactate MRS.

Results and Discussion Fig. 1 shows CBF and ADC images from a representative stroke animal. CBF decreased from 2.3 ± 0.54 ml/g.min in the contralateral normal area to 1.13 ± 0.57 ml/g.min in the ischemic lesion, representing a relative decrease of 52±19 % (P<0.01). pH-weighted MTR_{asym} was -4.3 ± 0.3% in the contralateral normal ROI, which decreased to -6.1 ± 0.6 % upon ischemia (P<0.01). In addition, ADC decreased from 0.72±0.03 to 0.56±0.03 μm^2/ms (P<0.01). Lactate was measured from an ROI within the ADC lesion. the ischemic lesion showed elevated lactate signal, with a Choline and Creatine normalized lactate peak (i.e., Lac/(Cho+Cr)) being 0.80 ± 0.21.

The ipsilateral ischemic ROI-based MTR_{asym} is plotted as a function of pH in Fig. 2. The lactate concentration [Lac] was calculated from PRESS MRS, with Creatine and Choline concentration being 4.79 and 9.35 mmol/kg, respectively (Florian et al., 1996). Tissue pH was estimated from the lactate concentration at pH=-0.0593·[Lac]+7.2, as shown by results of Chang et al. [8] in vivo MTR_{asym} was negative due to the baseline shift of $\Delta MTR'_{asym}$. K_{sw} was calculated using $ksw=5.57 \cdot 10^{pH-6.4}$ and two parameters, $\Delta MTR'_{asym}$ and f, were numerically solved from Eq. 2, being -7.44% and 1:867, respectively. We calculated the contralateral normal tissue pH from quantitative APT MRI, and overlaid it in Fig. 2 (open squares). This shows that the proposed quantitative pH MRI can reasonably describe in vivo APT MRI contrast, both contralateral normal and ipsilateral ischemic regions.

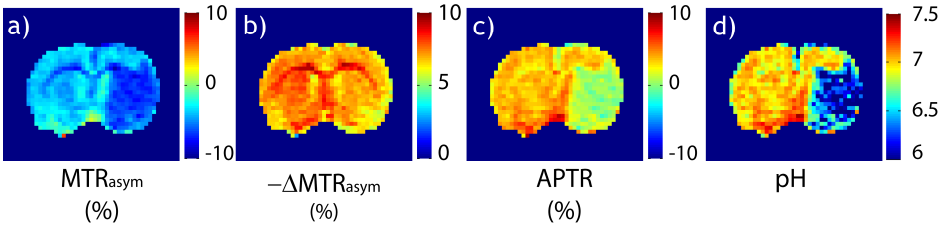

Fig. 3, Derivation from pH-weighted MTR_{asym} (a), ΔMTR_{asym} shift (b), pH-weighted APT MRI (c) and quantitative tissue pH (d).

Fig. 3 shows the calculation of quantitative tissue pH map from pH-weighted APT MRI. Because it has been shown that cerebral tissue R_{1w} increases with the MT contrast, the R_{1w}-scaled $\Delta MTR'_{asym}$ map was calculated (i.e. , $\Delta MTR'_{asym} = -7.44\% * 1.63/T_{1w}$), which displays hyperintense correction in corpus callosum (Fig. 3b). This effectively compensates the hypointensity over the corpus callosum in the MTR_{asym} map. Fig. 3c shows the endogenous APT map (i.e., $APTR=MTR_{asym} - \Delta MTR'_{asym}$). Indeed, the pH map clearly depicts tissue acidification in the ischemic lesion (Fig. 3d). Ischemic tissue pH estimated from APT MRI was 6.44 ± 0.24, in good agreement with that estimated from lactate MRS of 6.53 ± 0.18. In comparison, the contralateral normal tissue pH was 7.03 ± 0.05, and the pH difference between the ischemic and contralateral normal regions was -0.59 ± 0.22 (P<0.01).

References 1)Zhou et al., Nat. Med 2003; 9:1085-90. 2)Jokivarsi et al, MRM 2007; 57 (4):647-53. 3)Sun et al. JCBFM 2011; 65:1743-50. 4)Pekar et al. MAM 1996;35:70-79. 5)Hua et al. MRM 2007;58:786-93. 6) Mougin et al. Neuroimage 2010;49:272-81. 7) Sun et al. MRM 2007;57:405-10. 8) Chang et al. MRM 1990;13:6-13.