Stroke imaging based on amine-water proton exchange (APEX): correlations with ADC and metabolite concentrations

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Introduction: Chemical-exchange sensitive MRI techniques such as the off-resonance spin-locking (SL) or chemical exchange saturation transfer (CEST) techniques can be used to image pathological changes in tissue pH and protein/metabolite concentrations. With SL or CEST, the imaging contrast can be tuned to reflect dominantly slow or fast chemical exchange processes by using low power and long-duration or high power and short-duration radio-frequency irradiation pulses, respectively [1]. Recently, the amine-water proton exchange (APEX) effect has been proposed as a sensitive molecular imaging contrast at high magnetic field. The amine-proton is present in abundant free amino acids, as well as in amino-acid residues of protein and peptide side chains. While the APEX signal has been shown to exhibit higher contrast to noise ratio than the commonly used amide-proton transfer (APT) contrast [2] in a rat stroke model, its signal source is complex and not fully understood. In this preliminary work, we performed multi-parametric MRI and spectroscopic experiments to shed light to the signal source of the APEX contrast and investigated its potential applications in stroke studies.

Methods and Materials: All experiments were performed on a 9.4T Varian MRI system, with a volume coil for excitation and a surface coil for reception. MRI images were obtained with a multi-slice spin-echo (for ADC and APEX) or double spin-echo (for R_2) EPI sequences with the following parameters: in plane FOV=3.2×3.2 cm^2, matrix = 64×64, slice thickness = 2 mm, and number of slice = 4. For ADC, a low *b*–value of 5 s/mm^2 was applied on one axis, and a high *b*–value of 1200 s/mm^2 was applied on six different directions. For APEX, the spin-locking preparation pulses were applied at offsets = ±2.5 ppm from water frequency with irradiation power of 500 Hz for 150 ms. A spin-locking ratio asymmetry (SLR_{asym}) was calculated as $SLR_{asym} = [M(-2.5ppm) - M(2.5ppm)]/M_0$, where M(±2.5ppm) are the magnetization after the SL preparation and M_0 is the fully relaxed magnetization. A total of fifteen male Sprague-Dawley rats were scanned. Stroke was induced with middle cerebral artery occlusion (MCAO) on the left hemisphere. Apparent diffusion coefficient (ADC) and SLR_{asym} signals were measured in all rats while localized proton spectroscopy were measured in ten of the rats. Proton spectra were obtained using a short echo-time (TE) STEAM sequence [3] with TE/TR = 4/3000 ms and voxel size 3×3×3 mm^3. Voxels were chosen to cover either the center of lesions in ADC images or their corresponding contra-lateral regions. Metabolite concentrations were quantified with QUEST in jMRUI (http://www.mrui.uab.es/mrui) and normalized using unsuppressed water signal. Regions of interest (ROI) for the correlation analysis of ADC versus SLR_{asym} were defined as the hyper-intensity area in SLR_{asym} maps. Regions of interest for the correlation analysis of SLR_{asym} versus lactate concentration (n_{Lac}) were defined as voxels that overlap with the voxel in STEAM.

Results and Discussion:

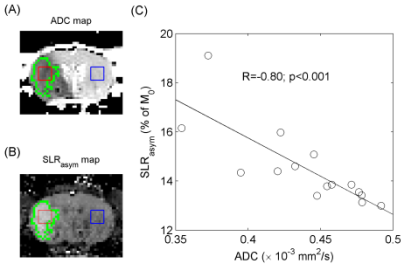

Figure 1: Representative ADC (A) and SLR_{asym} (B) maps after MCAO. The green contour denotes the defined ROI for correlation analysis of ADC versus SLR_{asym}. The red and blue boxes are voxels for spectroscopy studies on ipsi- and contra-lateral stroke sides, respectively. (C) Scatter plots of ROI averaged ADC versus SLR_{asym} values. Each data point

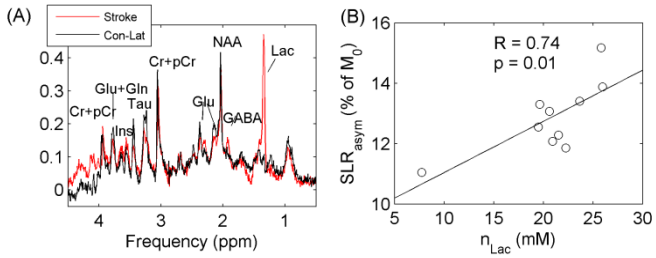

Figure 2: (A) Representative proton spectra acquired on stroke and contra-lateral brain regions. (B) Scatter plots of SLR_{asym} versus n_{Lac} on the stroke region. Each data point corresponds to the measurement at 1st hour in a different rat.

Figure 1 (A) and (B) show ADC and SLR_{asym} images, respectively in a representative rat. ADC is reduced in the stroke area while SLR_{asym} is enhanced. The enhanced SLR_{asym} reflects slowing down of amine-water proton exchange with reduced pH due to lactate acidosis after MCAO. There is a clear mismatch on the spatial extent of the lesions identified on the two maps, suggesting that ADC and SLR_{asym} reflect different underlying physiologic changes. ADC lesion size is larger than SLR_{asym} lesion in about half of the rats while similar to SLR_{asym} in the other rats. Figure 1 (C) is a scatter plot of region-of-interest (ROI) averaged SLR_{asym} versus ADC values, which are strongly correlated with each other with correlation coefficients (R) of -0.81 (p<0.001). Higher SLR_{asym} and lower ADC values are likely associated with more severe tissue damage.

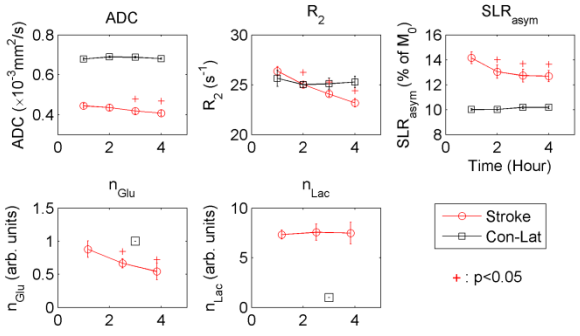

Figure 3: Temporal evolution of ADC, R_2, SLR_{asym}, n_{Glu}, and n_{Lac} after MCAO. Error bars are standard errors of the group mean. +: p<0.05 in a paired t test compared to the data point acquired at 1st hour

Figure 2 (A) shows representative spectra acquired on the stroke and contra-lateral sides, respectively in one animal. The lactate peak at ~1.3 ppm is dominant on the stroke side while almost invisible on the contra-lateral side. There are also clear enhancement and reduction of GABA and glutamate concentrations, respectively. Figure 2 (B) shows the strong correlation between SLR_{asym} and n_{Lac} across animals. The strong correlation shows that SLR_{asym} is sensitive to tissue pH changes.

Figure 3 displays the evolution of ADC, R_2, SLR_{asym}, n_{Lac} and glutamate concentrations (n_{Glu}). Comparing to the contra-lateral hemisphere, large ADC, SLR_{asym}, n_{Lac} changes occurred early after MCAO, when R_2 and n_{Glu} changes were still negligible. The concurrent large changes of SLR_{asym} and n_{Lac} indicate that the observed initial hyper-intensities in SLR_{asym} images mostly reflect the tissue pH decrease. SLR_{asym} decreases with time after initial enhancement although n_{Lac} remains constant, suggesting gradual concentration decrease of metabolites with appropriate APEX rates, such as glutamate [1]. Because SLR_{asym} depends both on APEX and R_2 and increases with decreasing R_2, its time-dependent change is expected to be more gradual compared to metabolite concentration changes.

Conclusions: The APEX signals are sensitive to tissue pH and are also correlated with metabolite concentration (Lac, Glu) changes in a rat stroke model. The initial sensitivity to pH and later to metabolite concentration variations suggest that APEX may serve as a useful biomarker for stroke applications and provide complementary information to current available techniques.

References: [1] T. Jin et al., NeuroImage, in press. [2] J. Zhou et al., Nat. Med. 9:1085 (2003). [3] I. Trac et al., MRM 41:649-656 (1999).