Characterization of tissue acidosis response in transient acute ischemic stroke with pH-sensitive APT MRI

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Introduction Ischemic tissue suffers a cascade of molecular, metabolic and structural damages after acute stroke[1]. Prompt reperfusion is vital to salvage the viable ischemic tissue prior to irreversible damage. Whereas perfusion and diffusion MRI have been widely used in stroke imaging with their lesion mismatch likely identifies the salvageable ischemic tissue (penumbra), it has been recognized that perfusion lesion overestimates the ischemic tissue while the diffusion lesion is partially salvageable with prompt treatment. Recently, pH-sensitive endogenous amide proton transfer, a variant of CEST MRI, has been developed. APT MRI remains promising to serves as a surrogate metabolic imaging marker for ischemic tissue classification [2-5]. Our study aims to evaluate the heterogeneous ischemic tissue injury and response to early reperfusion with multi-parametric MRI.

Materials and Methods Animal model: Transient middle cerebral artery occlusion (MCAO) was induced in adult male Wistar rats (n=10). Filament was removed 90 min post-MCAO. MRI and MRS: All experiments were conducted at 4.7T after acute MCAO. We acquired perfusion (ASL, TR/TS/TE=6500/3250/14.8ms, B_1=4.7 μT, NSA=32), APT (NSA1/NSA2=8/32, TR/TE=6500/14.8ms, B_1=0.75 μT), diffusion (TR/TE=3250/54ms, b=250 and 1000 s/mm^2, NSA=16), T_1 (inversion recovery sequence, inversion time from 250 to 3000 ms, NSA=4) and T_2 (SE MRI, TR/TE1/TE2=3250/30/100 ms, NSA=16) MRI. We obtained in vivo MRS using point-resolved single voxel spectroscopy (PRESS) from a cubic region of interest (ROI) of 3.5x3.5x3.5 mm^3, positioned approximately in striatum, which often displays ischemic lesions in MCAO model; the total acquisition time was approximately 17 min (TR/TE=2,000/144 ms, NAE=512). Images were acquired before and immediately after reperfusion. Data Analysis: MRS spectra were processed with java-based Magnetic Resonance User Interface (jMRUI), and images were processed in Matlab (Mathworks, Natick, MA). Tissue pH was calculated as $pH=6.4+\log_{10}(R_{1w}/f_s*(\alpha*(1-\sigma)/(MTR_{asym}-\Delta MTR'_{asym})-1)/5.57)$ from pH-weighed MRI, where α is the labeling coefficient, σ is the RF spillover factor, MTR_{asym} is pH-weighed APT asymmetry and $\Delta MTR'_{asym}$ is the native asymmetry shift (i.e. -7.4%) [7].

Results Fig. 1 shows a representative acute MCAO rat during MCAO and immediately after reperfusion. MCAO induces severe hypoperfusion in the ipsilateral ischemic side, which also displayed significant pH and diffusion deficits. Note that pH deficit is heterogeneous. Upon reperfusion, both CBF and pH showed substantial recovery. DWI lesion size decreased, consistent with the fact that early tissue injury in DWI lesion is heterogeneous and partially reversible, if treated early and effectively. Interestingly, the DWI lesion after reperfusion co-localizes with the region that displayed the most severe pH deficit. Notably, whereas pH was correlated with lactate concentration during acute stroke, the change of lactate upon reperfusion was not significant, suggesting different extrusion mechanism of H^+ from lactate [4]. In summary, our data showed that pH MRI may not only refine the PWI/DWI mismatch for delineating metabolic penumbra from benign oligemia, but also remains promising to stratify the heterogeneous DWI lesion.

	Contralateral Normal ROI		Ipsilateral Ischemic ROI	
	MCAO	**Reperf.**	**MCAO**	**Reperf.**
Lac/(Cho+Cr)	-	-	0.80±0.22	0.83±0.39
CBF	2.30±0.54	2.28±0.69	1.13±0.57	1.77±0.64*
$CESTR_{asym}$ (%)	-4.3±0.3	-3.8±0.7*	-6.1±0.6	-4.9 ± 0.9*
pH	7.0±0.05	7.08±0.01*	6.4±0.22	6.7 ± 0.24*
ADC (μm^2/ms)	0.72±0.03	0.73±0.03	0.56±0.03	0.60±0.07*
T_1 (s)	1.53±0.06	1.53±0.05	1.63±0.07	1.70±0.11*
T_2 ms)	56.4±2.0	56.8±0.8	55.0±1.1	61.6±3.7*

Table 1. Multi-parametric MRI of ischemic tissue response to reperfusion. There was substantial increase in CBF, pH-weighted MRI and ADC while lactate content showed very little change after reperfusion.

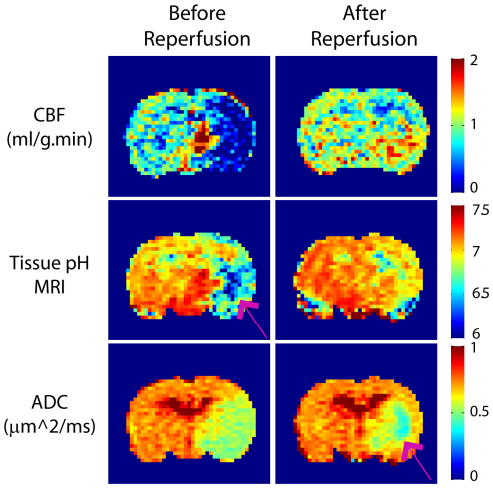

Fig. 1, Multi-parametric MRI of transient MCAO (90 min). CBF and pH recovered reasonably well. DWI lesion decreased and matched reasonably well with the most acidic pH lesion.

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