Association between pH-weighted endogenous amide proton transfer (APT) MRI and tissue lactic acidosis during acute stroke

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Introduction During acute stroke, anaerobic respiration is initiated subsequent to hypoxia and severe hypoperfusion. Because sufficient energy metabolism is vital for cell viability and salvageability, it is important to characterize metabolic impairments by monitoring alteration in energy substrates, neuronal biomarkers and tissue pH during acute stroke1–3. Endogenous amide proton transfer (APT) MRI, a variation of chemical exchange saturation transfer (CEST) imaging, is sensitive to tissue pH, and has been increasingly applied for studying ischemic stroke4–8. Here, we evaluated acute stroke with 1H MRS and multi-parametric MRI, and tested whether pH-weighted endogenous APT MRI may serve as a surrogate metabolic imaging marker for lactic acidosis.

Materials and Methods Animal model: Permanent middle cerebral artery occlusion (MCAO) was induced in adult male Wistar rats (n=10), approved by subcommittee on research animal care. Animal physiology was monitored online (heart rate and blood pO2), with body temperature maintained within its normal range. In addition, plasma glucose level was sampled immediately before MCAO. MRI: All experiments were conducted at 4.7T. Point-resolved spectroscopy (PRESS) was obtained from a region of interest (ROI) of 3.5 mm3 (TR/TE=1000/144ms, Na=1024) within the DWI lesion. Multi-parametric perfusion, diffusion, pH-weighted APT, T1 and T2 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)1, APT (Na1/Na2=8/32, TR/TE=6500/14.8ms)7, diffusion (TR/TE=3250/54ms, b=250 and 1000 s/mm2, Na=16)2, T1 (inversion recovery, TI from 250 to 3000 ms, Na=4) and T2 (SE MRI, TR/TE1/TE2=3250/30/100 ms, Na=16).

Data Processing: MRS was processed using java-based magnetic resonance user interface (jMRUI) while MRI data were processed in Matlab. Paired t-test was applied to assess the significance of change in MRS metabolites and MRI parameters.

Results and Discussion Fig.1 shows CBF, ADC and pH-weighted APT images (CESTRsym) from a representative stroke animal. Fig.2 shows MRS, from the ipsilateral ischemic lesion (black) and the contralateral control area (gray). Metabolites were normalized to the creatine and choline signal (i.e., Lac/(Cr+Cho)). Lactate was elevated in the ischemic lesion (0.90 ± 0.35), which was not measurable in the contralateral area. In addition, subtle decrease of NAA was found (0.79±0.17 vs. 1.10±0.23, p=0.012), consistent with the notion that NAA loss is an early marker of neuronal damage. In addition, CBF decreased from 0.75±0.13 to 0.29±0.12 ml/g.min (P<0.0001), and ADC decreased from 0.76±0.01 to 0.59±0.07 μm2/ms (P<0.0001). Moreover, pH-weighted APT/CESTRsym decreased from -3.8±0.7% to -5.9±0.7%, indicating tissue acidosis (P<0.0001). Furthermore, T1 increased from 1.52±0.07 s to 1.67±0.07 s (P<0.0001) while no significant change in T2 was found, being 55.4±2.2 and 55.8±2.7 ms, respectively (P=0.45).

We evaluated the association between lactate content and MRI parameters (Fig. 2). No significant correlation was found between T1 (R2=0.21, Significance F=0.18) and T2 (R2=0.01, Significance F=0.75) with lactate. In addition, the correlation between CBF and lactate was not significant (R2=0.02, Significance F=0.70). Importantly, both ADC (R2=0.50, Significance F=0.02) and pH-weighted APT/CESTRsym (R2=0.55, Significance F=0.01) correlated with lactate content, indicating that the severity of diffusion reduction and tissue lactic acidosis are associated with tissue lactate. It is important to note that the correlation between pH-weighted MRI and lactate was significantly improved when the T1 effect was taken into account, (i.e. CESTsym/T1), calculated as R2=0.71 and Significance F<0.005. This is consistent with the fact that CEST contrast scales approximately with T1, and therefore, T1-normalized APT contrast can more accurately assess tissue pH change. While on the other hand, no significant correlation was found between lactate content and pre-MCAO glucose level, likely due to variation in MCAO preparation and a relatively narrow range of glucose in young and healthy animals.

Our study characterized heterogeneous ischemic tissue damage with 1H MRS and multi-parametric MRI. We showed that pH-weighted endogenous APT and diffusion MRI correlate with lactate content, while no such relationship was found for perfusion and relaxation MRI. As such, our data demonstrate that pH-weighted MRI, by sensitizing to tissue acidification, provides a surrogate imaging marker of lactic acidosis, which may augment commonly used stroke diagnostic imaging techniques for improved characterization of heterogeneous ischemic tissue damage.