Quantitative Measurements of Amide Proton Transfer (APT) Signals and Tissue pH in Acute Ischemic Stroke

Dong-Hoon Lee[1], Xiaoguang Liu[2], Kai Zhang[1], Yi Zhang[1], Hye-Young Heo[1], Wenxiao Li[1], Raymond C. Koehler[2], and Jinyuan Zhou[1]

[1]*Division of MR Research, Department of Radiology, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States,* [2]*Department of Anesthesiology, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States*

Target audience: Researchers and clinicians who are interested in quantifying pH-weighted amide proton transfer (APT) imaging.

Purpose: Tissue damage after ischemic stroke has complex physiological and biological characteristics. Accurate tissue pH quantification using the APT-MRI technique has become an important research topic in recent years.[1-5] In this study, we demonstrate the feasibility of using extrapolated semi-solid magnetization transfer reference (EMR) signals to quantify APT signals and tissue pH in cerebral ischemia.

Methods: *MRI experiment*: Seven male Wistar rats were induced standard permanent middle cerebral artery occlusion (MCAO) by inserting a nylon suture into the lumen of the internal carotid artery to block the MCA, and scanned with 4.7T Bruker Biospec scanner at different times points (1h, 2h, and 5h) after MCAO. CEST dataset were acquired with a long continuous-wave RF saturation pulse (power = 1.3 μT, saturation time = 4 sec). Z-spectra with 61 frequency offsets were acquired: S_0 image and -15 to 15 ppm at intervals of 0.5 ppm. For B_0 corrections, WASSR dataset with 26 frequency offsets were acquired from -0.6 to 0.6 ppm at intervals of 0.05 ppm using 0.5 μT RF saturation power. In addition, high SNR APT images were acquired using two frequency offsets (±3.5 ppm) and sixteen signal averages. T_1, T_2, ADC, and CBF maps were also acquired.

Data processing: The B_0-corrected datasets were fitted to Henkelman's two-pool MTC model with the super-Lorentzian lineshape.[6] Only limited data points of large frequency offsets +7 ~ +15 ppm downfield from the water resonance were fitted to avoid possible CEST and NOE contributions. Experimentally observed T_{1w}^{obs} and T_{2w}^{obs} values were combined to fit the MTC modeling parameters. The EMR signals (Z_{EMR}) in the offset range from +15 ~ -15 ppm were obtained using fitted parameters, and the differences between Z_{EMR} and experimental data at 3.5 ppm and -3.5 ppm were used to calculate the APT and NOE signals (called APT$^{\#}$ and NOE$^{\#}$, respectively). Finally, to calculate tissue pH, the APTR equations [APTR = $(K_{sw}\cdot T_{1w}\cdot$[Amide proton] / [Water proton]$)\cdot(1-\exp-(t_{sat}/T_{1w}))$, pH = $6.4+\log_{10}(k_{sw}/5.57)$] were used under the assumption that the concentrations of amide protons and water protons remained constant.[1]

Results and Discussion: Using the EMR approach, the decrease in APT$^{\#}$ signals (at 3.5 ppm downfield from water) was clearly observed in the ischemic stroke (Fig. 1). The absolute NOE$^{\#}$ signals (peaked at 3.5 ppm downfield from water) seemed relatively larger than the absolute APT$^{\#}$ signals. However, the change in NOE$^{\#}$ signals was smaller (1h) or non-specific with respect to the offsets (2h, 5h). The presence of NOE$^{\#}$ made the MTR_{asym} to be negative, also less specific in both regions. The ADC, CBF, APT$^{\#}$, NOE$^{\#}$, MTR_{asym}, and pH maps showed large signal differences in the ischemic stroke lesion (Fig. 2), compared to the contralateral normal brain; however, the T_2 and T_1 maps showed subtle changes. The APT$^{\#}$ and MTR_{asym} signals were generally lower in the ischemic lesion than in the contralateral (Fig. 3). The calculated pH values were consistently lower in the ischemic stroke legion (pH ~6.69) during the initial hours after MACO.

Conclusion: The EMR provides a more accurate approach for quantifying APT signals and pH of the ischemic stroke tissue.

References: [1] Zhou et al. Nat. Med. 2003. [2] Sun et al. JCBFM 2008. [3] Jin et al. MRM 2013. [4] McVicar et al. JCBFM 2014. [5] Zaiss et al. NMR Biomed 2014. [6] Henkelman et al., MRM 1993.

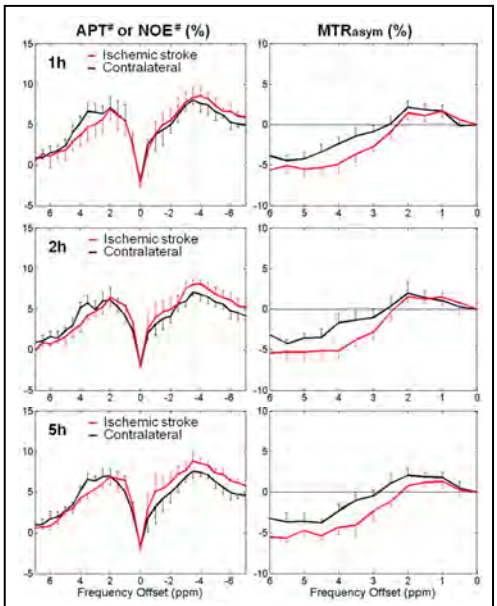

Fig. 1. APT$^{\#}$ and NOE$^{\#}$ signal features (left column), and the commonly used MTR_{asym} spectra (right column) as a function of time after MCAO (n = 7).

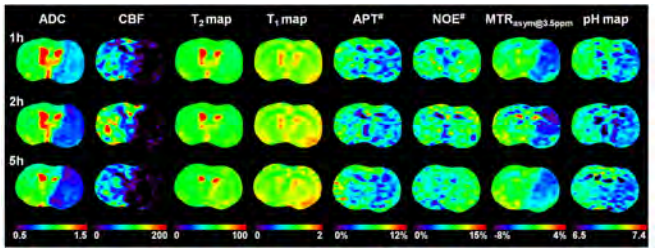

Fig. 2. Calculated multi-parametric MR images for a typical rat.

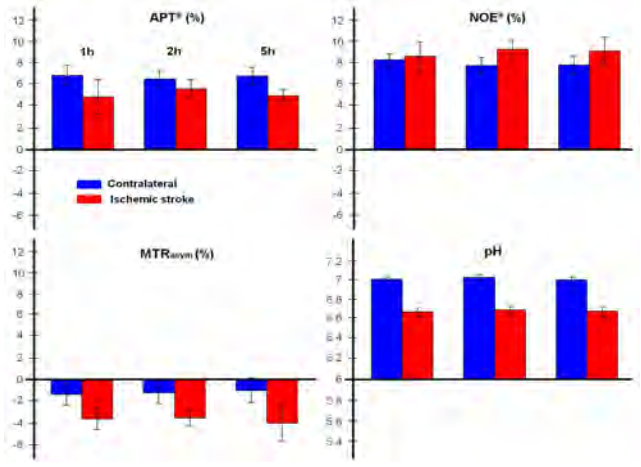

Fig. 3. APT$^{\#}$, NOE$^{\#}$, MTR_{asym}(3.5ppm), and tissue pH as a function of time after MCAO.