Effects of Water Proton Concentration and Water T1 Changes on APT and NOE Imaging Signals in Gliomas

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Target audience: Researchers and clinicians who are interested in the quantification and applications of CEST imaging.

Purpose: Amide proton transfer (APT) imaging can provide endogenous contrast related to the mobile amide proton concentration, the amide proton exchange rate (depending on tissue pH), and several other possible tissue and experimental parameters (e.g., proportional to the water longitudinal relaxation time or T_{1w}, and inversely proportional to water proton concentration).[1] Thus, one important issue to be evaluated is how water concentration and water T_1 affect the observed APT signal intensity in tissue. The purpose of this study is two-fold: to quantify APT using a more accurate mathematical approach based on extrapolated semi-solid magnetization transfer reference (EMR) signals, and to investigate the correlations between APT and other parameters (water proton concentration and T_{1w}).

Methods: *MRI experiment*: Thirteen human glioblastoma (hGB)-bearing rats and eleven U87-bearing rats were scanned at 4.7T. CEST datasets were acquired with a long continuous-wave RF saturation pulse (power = 1.3 μT, time = 4 s). 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 map with seven inversion recovery times (0.05~3.5 s), T_2 map with seven TEs (30~90 ms), and isotropic ADC with seven b-values (0~1000 s/mm^2) were also acquired.

Data processing: The B_0-corrected datasets were fitted to Henkelman's two-pool MTC model with the super-Lorentzian lineshape.[2] Only limited data points of large frequency offsets +7 ~ +15 ppm downfield 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 whole offset range from +15 ~ -15 ppm were obtained or extrapolated 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). T_{1w} was fitted with $I = I_0 + B \cdot \exp(-TI/T_{1w})$, and we assumed that [water proton] ≈ I_0.

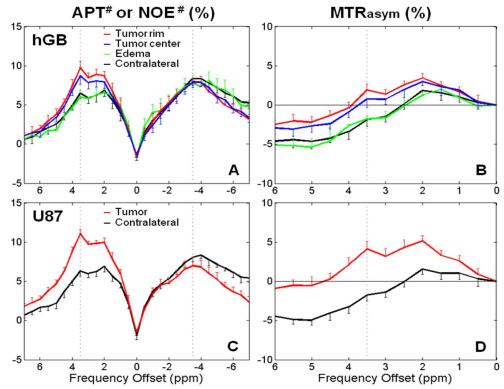

Fig. 1. Calculated APT$^{\#}$ and NOE$^{\#}$ signal features (A and C) and the commonly used MTR_{asym} spectra (B and D) for two tumor models (hGB and U87).

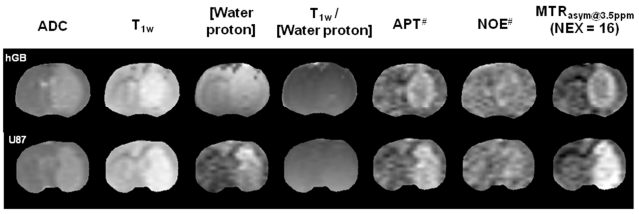

Fig. 2. ADC, water T_1 (T_{1w}), water proton concentration, T_{1w}/water proton concentration, APT$^{\#}$, NOE$^{\#}$, and $MTR_{asym@3.5ppm}$ for two tumor models.

Results: Using the new EMR approach, the large APT$^{\#}$ signal at 3.5 ppm downfield, amine CEST$^{\#}$ signal at 2 ppm downfield, and NOE$^{\#}$ signal at about -3.5 ppm upfield were clearly observed in both animal models (Fig. 1). Notably, APT$^{\#}$ signal intensities (>10% of the bulk water signal) of glioma were much larger than the values reported before.[1] On ADC, T_{1w}, [water proton], APT$^{\#}$, and MTR_{asym} maps (Fig. 2), both tumors showed hyperintensities, compared to the contralateral normal brain tissue. However, T_{1w}/[water proton] maps showed negligible signal differences between the tumor and contralateral regions. Notably, APT$^{\#}$, NOE$^{\#}$, and MTR_{asym} values showed no significant correlations with T_{1w}/[water proton] (all $p > 0.05$; Fig. 3). These experimental results clearly showed that the APT effects observed in these two glioma models were not associated with the combined effects of water concentration and T_{1w}.

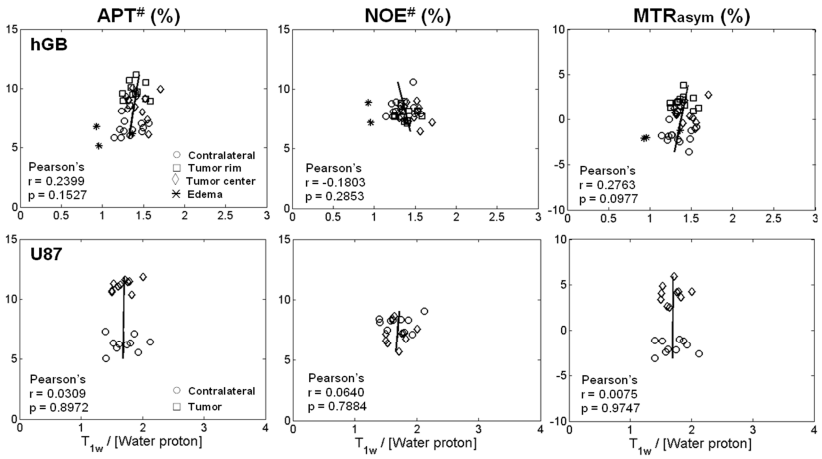

Fig. 3. Correlation analysis of APT$^{\#}$, NOE$^{\#}$ and MTR_{asym} with T_{1w}/water concentration.

Discussion and Conclusion: Although the water content is usually higher, and water T_1 is enhanced in the tumor, it is extremely important to understand that these two changes are mostly compensated for in the tumor and many other diseases.[1] Therefore, assessing the influence of water T_1 on APT and NOE imaging *in vivo* should be performed cautiously. Our results indicated that the observed APT hyperintensities in the tumor is primarily related to the mobile amide proton content and/or the amide proton exchange rate. The findings would be very helpful for the understanding of the APT-MRI contrast mechanism in clinical applications.

References: [1] Zhou et al., Nat. Med. & MRM 2003. [2] Henkelman et al., MRM 1993.