Assessment of Amide Proton Transfer and Nuclear Overhauser Effects using long RF Saturation at 3T in Clinical Brain Tumor Applications

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Purpose – APT[1-4] is an emerging MRI technique for sensitive tissue characterization via an assessment of the local concentration of mobile proteins in cells. Clinical applications are particularly foreseen in oncology, e.g. for differential diagnosis of tumors (grading[4]) and for therapy follow-up[3]. Recently, a number of clinical studies[4,5] have been published related to APT in neuro oncology applications, where APT is analyzed based on magnetization transfer asymmetry (MTR_{asym}), comparing negative and positive saturation frequency offsets (±3.5ppm). MTR_{asym} can be robustly and efficiently measured in clinical settings, including 3D acquisitions with large coverage in less than 5 minutes[5,6]. On the other hand, MTR_{asym} may be biased by nuclear Overhauser effects (NOE) at opposite frequency offsets[7-9]. The influence of NOE effects may strongly depend on the main magnetic field (B_0) and on saturation parameters. Most reported studies were performed at $B_0 \geq 7T$[8,9] and typically employed short RF saturation (T_{sat}<1s) and low saturation field amplitudes (e.g. $B_{1,rms}$=0.5µT)[7]. Here, a previously proposed APT protocol ($T_{sat}/B_{1,rms}$=2s/2µT) on 3.0T MRI systems[4] is applied for human brain tumor cases and analyzed for NOE contributions using improved Z-spectral fitting methods. It was hypothesized, that there is only a negligible NOE contrast between NAWM and tumor tissue for this protocol at 3T.

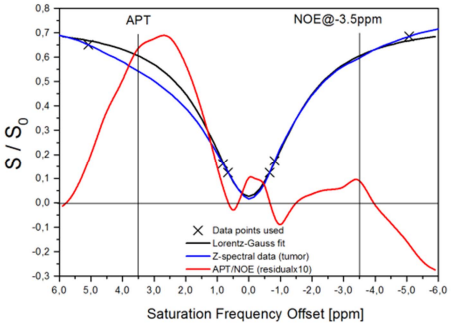

Figure 1: Z-spectral analysis for the separation of APT and NOE effects in a tumor tissue region. 6 selected data points were used for a Lorentz-Gaussian fit of the symmetric MTR background.

Methods – This study was performed on APT imaging data of 15 patients with brain tumors (47±18 years old, 10 males and 5 females), from whom informed consent was obtained. Histology confirmed types of the tumors were as follows: 5 metastases of multiple origins, 5 low grade glioma (LGG), 5 high grade glioma (HGG). A 3.0T MRI scanner (Achieva TX, Philips Healthcare, Netherlands) with 2-channel body coil transmission and 8-channel head coil reception was used with the following parameters: 40×50ms sinc-gaussian saturation (100% duty cycle by alternated transmission[10]), $B_{1,rms}$=2µT, 25 Z-spectral images $S[\omega]$ (ω=–6…6ppm, step 0.5ppm, and S_0, ω=–1560ppm), 2D single-shot fast spin-echo (TSE), driven equilibrium refocusing, sensitivity encoding R=2, FOV 230 × 230mm^2 , voxel size 1.8 × 1.8 × 5 mm^3, TR/TE = 5s/6.2ms, acquisition time 2½ min. A gradient-echo ΔB_0 map (ΔTE=1ms) was acquired separately to calculate B_0 corrected, interpolated Z-spectra $\check{S}[\omega]$ (steps 0.165 ppm). In extension to previous Z-spectral methods[11], a Lorentz-Gauss function (Eq.1) with 4 degrees of freedom (A: Amplitude; w_e: Gauss/Lorentz relative weights; w_1: Gaussian width; w_2: Lorentzian width; boundary condition: 0.5< w_e <0.95) was used to model the symmetric MTR background. 6 z-spectral points were chosen as support: ±5.10, ±0.82, ±0.66 ppm – excluding the actual spectral APT and NOE regions. Non-linear least square fitting was based on mpfit[12], and voxel-wise fitting was implemented as a C++ plugin for ImageJ to create APT_{fit} and NOE_{fit} images by subtracting the fitted symmetric function from $\check{S}[\omega=\pm 3.5ppm]$ and $MTR_{asym} = APT_{fit} - NOE_{fit}$. For statistical analysis of the observed APT/NOE signal contributions, ROIs were defined for the apparent tumor area (TSE images) and for normal appearing white matter (NAWM) in the contralateral hemisphere. Paired t-tests were performed on the NOE data and the APT data in the tumor and normal regions.

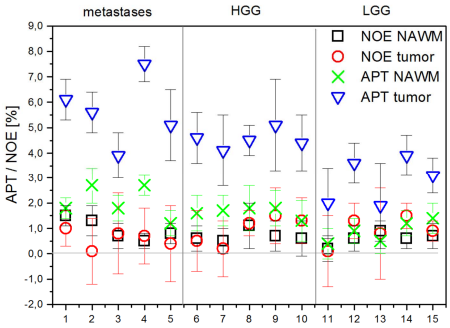

Figure 2: Overview of APT and NOE results of ROI analysis for N=15 brain tumor cases.

$$(1)\quad S[\omega]/S_0 = 1 - w_e\left[\frac{A}{w_1\sqrt{\frac{\pi}{2}}}e^{-2\frac{\omega^2}{w_1^2}}\right] - (1-w_e)\left[\frac{2A}{\pi}\frac{w_2}{(2\omega)^2+{w_2}^2}\right]$$

Results and Discussion – The applied fitting model was found to robustly fit the Z-spectra of various tissue compartments (NAWM, tumor, edema, cysts), while a simple Lorentzian shows variable fitting quality for different tissues and does not correctly model S[ω] for large ω (which should converge to S_0). Fig. 2 shows the summary of the ROI analysis performed on APT_{fit} and NOE_{fit} images for all tumor cases and Fig.3 shows an example case. The NOE_{fit} image apparently does not show a particular contrast between the tumor region and NAWM areas of the brain, except for some slight effects at the tumor edges (and boundaries to the CSF). The NOE values in tumor and NAWM are close and apparently not distinguishable within the error bars (standard deviation over the ROI). In case #2, the NOE effect in the tumor area appears to be lower than the value for NAWM, but here, the apparent tumor was dominated by a cystic component (small solid tumor area). The group mean values of NOE effects are $NOE_{fit,N}$=0.75±0.34% in NAWM and $NOE_{fit,T}$=0.82±0.49% in tumor tissue, respectively. On the other hand, for nearly all cases (except for #11 and #12 which are low grade), the APT values in the tumor region are significantly higher than in the normal control area. The group mean values of APT effects are $APT_{fit,N}$=1.5±0.7% in NAWM and $APT_{fit,T}$=4.4±1.5% in tumor tissue, respectively. The hypothesis that NOE_{fit} values do not show a contrast between tumor and NAWM regions, was confirmed by the t-test with a high probability level of P=0.66 (t=-0.46) using all 15 cases. These results contradict previously published conclusions[7] that the tumor to NAWM contrast is mostly due to a loss of native MT asymmetry at 3T. In our study, an increased asymmetry is observed for tumor tissue.

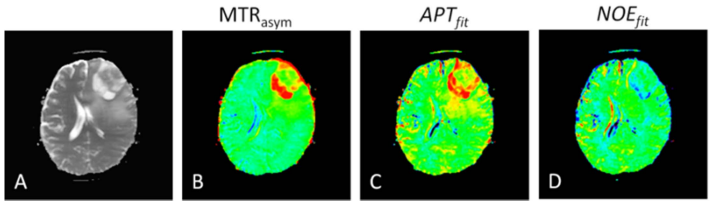

Figure 3: TSE (A), MTR_{asym} (B), $APT_{fit,+3.5ppm}$ (C) and $NOE_{fit,-3.5ppm}$ (D) images of a metastasis (case #5; -7%...7%). The NOE image shows low contrast throughout the brain, thus, APT_{fit} and MTR_{asym} images show very similar results.

Conclusion - The results indicate that MTR_{asym} in combination with a specific protocol at 3T may be used to assess APT signal levels in clinical applications without significant interference by NOE effects.

References – **1**. Zhou J et al., Nat Med.9:1085(2003). **2**. Wen Z et al., Neuroimage 51:616(2010). **3**. Zhou J et al., Nat Med.17:130 (2011). **4**. Togao O et al. Neuro Oncol. 2014 Mar;16(3):441. **5**. Jones CK et al. MRM 56, 585 (2006). **6**. Keupp J et al., Proc. ISMRM 22:3150(2014). **7**. Scheidegger R et al. Neuroimage 99:256 (2014). **8**. Xu J et al. Biomed. 27(4):406-16 (2014). **9**. Liu D et al. MRM 70(4):1070 (2013). **10**. Keupp J et al., Proc. ISMRM 19:710(2011). **11**. Jones CK et al. MRM 67:1579 (2012). 12. Markwardt CB et al. 2009: http://purl.com/net/mpfit