On the origins of chemical exchange saturation transfer (CEST) contrast in tumors at 9.4T

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Target Audience: Investigators who are interested in the biophysical mechanism of chemical exchange saturation transfer (CEST) imaging in oncology and its use in probing tumor microenvironment.

Purpose: It has been suggested that amide proton transfer (APT) imaging, a specific form of chemical exchange saturation transfer (CEST) imaging, detects endogenous amide protons with a resonance frequency offset 3.5 ppm downfield from water, and thus may be sensitive to variations of mobile proteins/peptides in tumors[1]. However, CEST measurements are influenced by various confounding effects, such as spillover, magnetization transfer (MT), MT asymmetry and longitudinal relaxation, so the mechanism or degree of changed APT signals in tumors are not certain. In addition to APT, nuclear Overhauser enhancement (NOE) effects upfield from water may also provide distinct information about tissue composition but suffer from confounding effects. In the current study, a three-offset 1/Z method was introduced to detect tumors, which provides a new intrinsic inverse metric to correct the influence of spillover, MT and R1 (spin-lattice) relaxation. The results may assist elucidating the origins of APT and NOE contrasts in tumors.

Methods: *Theory*: APT contrast is usually characterized by the CEST asymmetry[1], i.e. $MTR_{asym}(3.5\ ppm)=Z(-3.5)-Z(3.5)$. An alternative three-offset method[2] for APT contrast was proposed to reduce the dependence on MT asymmetry as $APT^{*}=Z_{ref}(3.5)-Z(3.5)$, where $Z_{ref}(3.5ppm)=[Z(4.0)+Z(3.0)]/2$. The 1/Z method[3] has also been proposed in which

$$MTR_{Rex}(\Delta\omega)=\frac{1}{Z(\Delta\omega)}-\frac{1}{Z_{ref}(\Delta\omega_{ref})}=\frac{R_{ex}}{\cos^2\theta\cdot R_{1a}} \quad \text{and} \quad AREX(\Delta\omega)=MTR_{Rex}(\Delta\omega)\cdot R_{1a}=R_{ex}/\cos^2\theta\,.$$

R_{ex} is the exchange-dependent relaxation rate in the rotating frame. In order to further reduce MT asymmetric effect *in vivo*, we propose a revised 1/Z method in the current study which combines the original 1/Z method[3] and the three-offset method[2], namely,

$$MTR_{Rex}(APT)=\frac{1}{Z(3.5)}-\frac{2}{Z(4.0)+Z(3.0)}=\frac{R_{ex}(APT)}{\cos^2\theta\cdot R_{1a}},\quad AREX(APT)=MTR_{Rex}(APT)\cdot R_{1a}\approx R_{ex}^{APT}=k_a(APT)$$

$k_a(APT)$ is the chemical exchange rate from water to the amide proton pool. Note that the metrics for NOE quantification can be obtained in a similar way, namely,

$$MTR_{Rex}(NOE)=\frac{1}{Z(-3.5)}-\frac{2}{Z(-2.0)+Z(-3.0)}=\frac{R_{ex}(NOE)}{\cos^2\theta\cdot R_{1a}},\quad AREX(NOE)=MTR_{Rex}(NOE)\cdot R_{1a}\approx k_a(NOE)$$

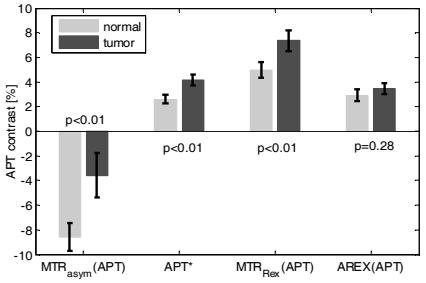

Fig.1 Summary of four APT parameters, i.e. MTR_{asym}, APT*, MTR_{Rex}(APT) and AREX(APT), of all eight rats to differentiate tumors from normal tissues.

Animal and cancer model: Eight F344/Hsd rats were injected with 9L glioma cells in their right brain hemispheres to allow tumors to grow to 30-40mm^3.

In vivo imaging: All experiments were performed on a 9.4T Varian MRI scanner. CEST images were acquired with continuous wave saturation pulses (1μT for 5 seconds), and all Z-spectra were normalized and corrected for B_0 inhomogeneities using WASSR. Maps of relaxation rates $R_1(=1/T_1)$ were obtained using inversion recovery followed by spin echo EPI acquisition. All images were obtained using a 2-shot echo-planar imaging sequence with 333μm in-plane resolution and NEX=2.

Results and Discussion: Fig.1 shows that only the conventional MTR_{asym}(APT) show negative values in both tumor and contralateral normal tissue, indicating that there is a significant influence of the MT asymmetric effect in MTR_{asym}(APT). Both APT* and MTR_{Rex}(APT) show significantly higher values in the tumor ($p<0.01$ given by the Wilcoxon rank-sum test). However, AREX(APT), with the correction for R_1 relaxation, shows no significant difference between tumor and normal tissue ($p=0.28$). By contrast, Fig.2 shows NOE* obtained using the three-offset method does not distinguish tumors from contralateral normal tissues ($p=0.33$), whereas both MTR_{Rex}(NOE) and AREX(NOE) show significantly lower values in the tumor compared to normal brain ($p < 0.01$).

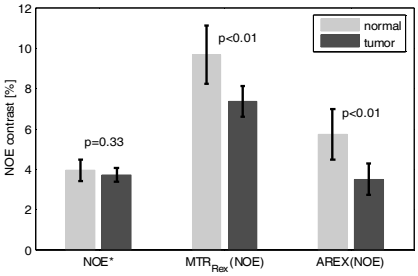

Fig.2 Summary of three NOE parameters (NOE*, MTR_{Rex}(NOE) and AREX(NOE)) of all eight rats to differentiate tumor from normal tissue.

Conclusion: After corrections for spillover, MT and R_1 effects, corrected APT in tumors was found not significantly different from normal tissues, but corrected NOE effects in tumors showed significant decreases compared with normal tissues. These results are consistent with biochemical measurements[4] suggesting that there is no significant enhancement of protein contents in the tumors. The remarkable influence of R_1 relaxation on both APT and NOE measurements indicates the need for mapping and correcting for variations in relaxation rates to obtain reliable CEST measurements. Our results may assist better understanding the contrast depicted by CEST imaging in tumors, and the development of improved APT and NOE measurements for cancer imaging.

References: (1) van Zijl et al. MRM 2011 (2) Jin et al. MRM 2013 (3) Zaiss et al. NBM 2013 (4) Xu et al. ISMRM. 2012