In vivo T_2^* effect on pharmacokinetic parameter estimation using reference tissue arterial input function at 7T

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Introduction: In T_1-weighted dynamic contrast enhanced magnetic resonance imaging (DCE-MRI), it is typically assumed that T_2^* remains constant. But at high field strength, such as 7T, changes in T_2^* during contrast agent passage may not be negligible. The influence of T_2^* on lesion signal intensity and arterial input function (AIF) can induce systemic errors in pharmacokinetic parameter estimation [1,2]. An AIF measured from a major vessel could be substantially affected due to its high Gd concentration. In comparison, when a reference tissue, such as muscle, is used for AIF estimation, the effect of T_2^* change may be relatively smaller than that of directly measured AIF. To date, however, it has not been shown how the T_2^* variation during DCE-MRI can affect the kinetic model analysis using reference tissue AIF. Thus, the aim of this study was to investigate changes in T_2^* of tumors by Gd-based contrast agent at 7T and its effect on kinetic model analysis.

Materials and Methods: Six- to eight-wk-old BALB/c mice with 4T1 (n = 8) breast cancer xenografts were scanned using a 7T horizontal bore magnet with a volume transmit and receive coil. General anesthesia was induced by 1.5% isoflurane in air. The animal was mounted on a cradle with respiratory and temperature monitoring probes. The animal body temperature was maintained at 33 ± 2 ºC during the scan. A 3D multiple gradient echo (MGE) sequence was used to acquire two echoes per excitation ($TR/TE_1/TE_2$=12ms/2.5928ms/6.7928ms, image matrix = 128x128x9, resolution = 0.25x0.33x2mm, temporal resolution = 7.776s). This sequence was run to acquire 60 3D images for about 8 min with flip angle 15°. A bolus of 10 mM Gd-DTPA in saline, corresponding to dose of 0.1 mmol/kg, was injected through a tail vein catheter starting 1 min after the start of data acquisition. This study was approved by the institutional animal care and use committee.

Regions of interest (ROI) were selected for muscle and enhancing region of tumor in each mouse (Figure 1a). The average of voxels from the muscle and lesion ROIs were used for the analysis. T_2^* curves (Figure 1b) were computed by taking the ratio of echo 1 and echo 2 signal intensity curves from the DCE-MRI data

$$S_{echo\ 1\ or\ 2}(t) = S_0\left(1-e^{-TR/T_1(t)}\right)e^{-TE_{1\ or\ 2}/T_2^*(t)}\cdot\sin(\alpha)\Big/\left(1-e^{-TR/T_1(t)}\cos(\alpha)\right) \qquad (1)$$

which leads to $T_2^*(t) = (TE_2 - TE_1)\Big/\ln\left(S_{echo1}(t)/S_{echo2}(t)\right)$. T_2^* corrected lesion signal intensity was obtained by substituting the computed time-dependent T_2^* and its corresponding echo time into Equation (1). T_2^*-corrected and non-corrected AIFs (Figure 1c) were obtained by using the muscle ROI as a reference region (RR) and using the neural network approach previously reported [3]. K^{trans} and v_e of RR were assumed to be 0.11 min^{-1} and 0.20, respectively. The generalized pharmacokinetic model with vascular compartment was used for the kinetic model analysis to obtain volume transfer constant K^{trans}, interstitial volume fraction v_e, and vascular plasma volume fraction v_p. T_1 mapping performed by using an inversion recovery sequence with TR=12s and inversion times of 50ms, 500ms, 2.5s, 5s, and 8s.

Results: Figure 1c shows the muscle ROI signal intensity enhancement curves for echo 1, echo 2 and T_2^* corrected echo 1. The corresponding AIFs generated from the reference tissue signal intensity curves were also shown in Figure 1c. The corrected AIF had a higher signal level than the uncorrected AIF.

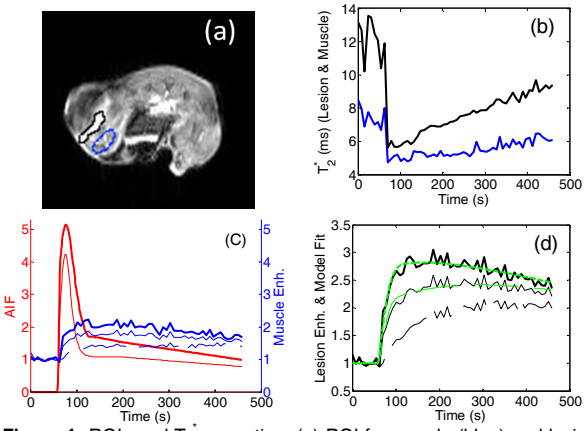

Figure 1: ROIs and T_2^* correction. (a) ROI for muscle (blue) and lesion (black). (b) T_2^* curves from double echo sequence; black for lesion ROI and blue for muscle ROI. (c) AIF from reference tissue and muscle ROI enhancement curves from echo 1 (thin red/blue solid), echo 2 (thin blue dash) and T_2^* corrected (thick red/blue solid). (d) Lesion enhancement curves from echo 1 (thin black solid), echo 2 (thin black dash) and T_2^* corrected (thick black solid), and corresponding model fit for echo 1 (thin green solid) and corrected (thick green solid).

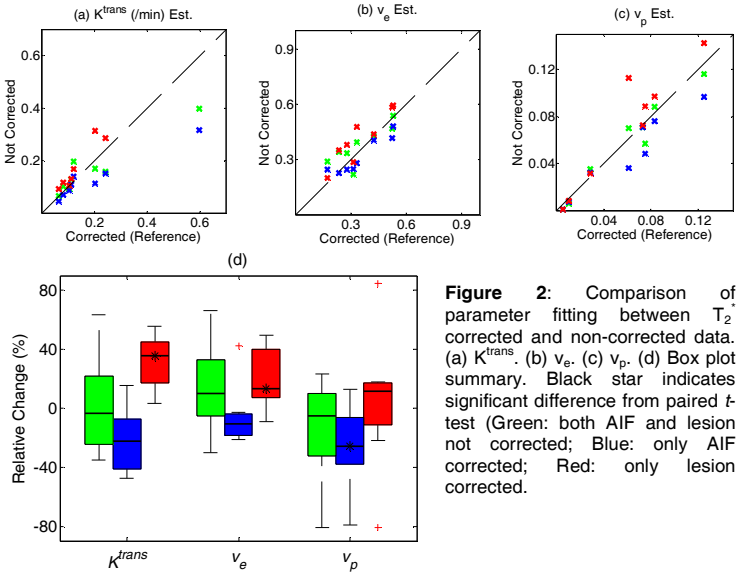

Figure 2: Comparison of parameter fitting between T_2^* corrected and non-corrected data. (a) K^{trans}. (b) v_e. (c) v_p. (d) Box plot summary. Black star indicates significant difference from paired *t*-test (Green: both AIF and lesion not corrected; Blue: only AIF corrected; Red: only lesion corrected.

Figure 1d shows lesion ROI enhancement curves from echo 1, echo 2 and T_2^* corrected echo 1. Extended GKM model fits for echo 1 and T_2^* corrected lesion signal intensity curves are shown in Figure 1d. Figures 2a, 2b, and 2c show comparisons between pharmacokinetic parameters (K^{trans}, v_e, and v_p) with and without T_2^* correction for both AIF and lesion. Parameter estimates from only AIF corrected and only lesion corrected data were also plotted for comparison. Figure 2d shows a box plot that represents a summary of comparisons for the above three cases. The parameters estimated using T_2^* corrected data for both AIF and lesion were used as the reference standards for comparison.

When T_2^* correction was not applied to both AIF and lesion, the median of kinetic parameters were within 11% of the reference standard values (green markers and bars in Fig.2d), and were not significantly different from the reference standard values (paired t-test, $p > 0.05$). When T_2^* correction was applied only to the AIF, the kinetic parameters were underestimated by up to 25.7% (blue in Fig.2d). The v_p values were significantly different ($p = 0.038$) from the reference value. In contrast, when T_2^* correction was applied only to the lesion data, the kinetic parameters were overestimated up to 35.7% (red in Fig.2d). Both K^{trans} ($p = 0.028$) and v_e ($p = 0.018$) were significantly different from the reference standard values. It is also noted that, among the three kinetic parameters, v_e had the smallest error ranges, which indicated that T_2^* effect probably had the least amount of influence on v_e estimation as v_e is more related to the curve washout portion.

Discussion: In this study, we have demonstrated that it is possible to correct for the T_2^* effect in T_1-weighted DCE-MRI experiments using a double-echo gradient echo sequence. Interestingly, the results of our study showed that, although T_2^* changes substantially affected the T_1-weighted signal intensity time curve, there was no significant difference between pharmacokinetic model parameters from the T_2^* corrected and non-corrected data. This may be because AIF and lesion curves are similar affected by T_2^* such that correction is not necessary for kinetic model analysis. This may not be true for the AIF directly measured from a major vessel where the T_2^* effect would be substantially higher than that in a lesion. Future studies are warranted to investigate the T_2^* effect with a larger cohort as well as in DCE-MRI studies for monitoring tumors undergoing treatment.

Reference:[1] Kleppesto M. M. et al, *Proc. Intl. Soc. Mag. Reson. Med.* 19 (2011); [2] Yu Y. et al, *Proc. Intl. Soc. Mag. Reson. Med.*19 (2011); [3] Zhang and Kim, *Proc. Intl. Soc. Mag. Reson. Med.*(2011).

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