Improved accuracy and precision in estimation of intracellular water liftime

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Introduction: Intracellular water lifetime (τ_i) is closely related to membrane permeability and intracellular water diffusivity in addition to size and shape of the cells [1, 2]. The importance of this parameter is paramount in understanding MR data, particularly for diffusion and perfusion experiments. Dynamic contrast enhanced (DCE)-MRI of a diffusible tracer has been widely used for diagnosis of cancer and monitoring treatment response. Our previous study showed the effect of water exchange on the MR contrast enhancement curve depends on MRI imaging parameters, such as flip angle [3]. Thus, we hypothesized that using multiple flip angles during DCE-MRI data acquisition could reduce the uncertainty in the estimation of intracellular water lifetime. In this study, we conducted a numerical simulation study as well as a preclinical study to test our hypothesis.

Materials and Methods: Numerical simulation was conducted to identify the optimal pair of flip angles for accurate measurement of τ_i. Realistic DE-MRI data were generated in two steps; calculation of contrast agent concentrations in tissue compartments with bolus injection and conversion to corresponding MRI signal curves. CA concentration curve was simulated using the MMID4 model (NSR, Univ. of Washington). The three-site two exchange (3S2X) model was used to simulate the effect of water exchange between tissue compartments. We assumed the DCE-MRI data acquisition used two flip angles; one flip angle (α_1) during the first half of bolus tracking and a different flip angle (α_2) for the second half. The generalized kinetic model (GKM) combined with water exchange model (WX) was used to fit the simulation data for estimation of kinetic model parameters including τ_i.

For the preclinical study, six- to eight-wk-old BALB/c mice with 4T1 (n = 3) and 67NR (n=3) 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 25 ± 2 ºC during the scan. A 3D FLASH sequence was used to minimize the flow effect (TR/TE=7.116/3.0 ms, image matrix = 128 x 128 x 10, resolution = 0.25 x 0.25 x 1.5 mm, temporal resolution = 5.16 s). This sequence was run to acquire 120 3D images for 11.8 min (70 frames for α_1 =15˚ and 50 frames α_2=25˚). A bolus of 10 mM Gd-DTPA in saline, corresponding to dose 0.1 mmole/kg, was injected through a tail vein catheter starting after the acquisition of 13 pre-contrast images (~ 1 min). This study was approved by the institutional animal care and use committee. Arterial input function (AIF) was obtained from a reference region (RR) in the muscle. K^{trans} and v_e of RR were assumed to be 0.11 min^{-1} and 0.20, respectively.

For cross-validation, τ_i measurement was also conducted using a constant-gradient DWI experiment. A stimulated echo diffusion weighted sequence was used with TR =2 s, TE = 32.7 ms, image matrix =128 x 64, resolution = 0.71 x 0.95 mm, diffusion gradient duration δ = 7 ms, and diffusion weighting gradient G = 150 mT/m. The sequence was run multiple times with a series of diffusion times; 15, 75, 100, 125, and 150 ms. A two compartmental model was used to describe a combination of hindered extracellular space and restricted intracellular space [4]. Assuming extracellular signal contributions were dephased completely with the large q value, the intracellular water lifetime was determined as the inverse of the slope of constant-gradient data [4].

Results and Discussion: The result of numerical simulation was assessed in terms of accuracy (estimated – true values) and precision (inter-quartile range, 25%-tile to 75%-tile). Figure 1a shows that using same flip angles for both α_1 and α_2 , i.e., single flip angle, is optimal for the accuracy of τ_i estimation. In contrast, the precision can be improved by using a smaller angle for α_1 and a larger angle for α_2, as shown in Figure 1b. Thus, we chose α_1 = 15˚ and α_2 = 25˚ as a trade off between the accuracy and precision. Figure 1c shows that the τ_i estimation using the two flip-angle method had better accuracy and precision than the conventional one flip-angle method.

Figure 2 shows an example of data from the mouse study to measure τ_i using DCE-MRI and DWI. The summary of the estimation results from six mice (Figure 3) suggests that the precision of τ_i estimation can be substantially improved by using two flip angles and there are also noticeable improvement in the accuracy.

The results of our study supports our hypothesis that the uncertainty of τ_i estimation can be reduced by using two flip angles for DCE-MRI data acquisition. Future study is warranted to investigate the feasibility of using other acquisition methods for further improvement in τ_i estimation.

Reference:[1] Quirk J.D. et al., *MRM*2003;50(3):493–499. [2] Norris D.G. *NMR Biomed* 2001;14(2):77-93. [3] Zhang and Kim, ISMRM 2010; [4] Pfeuffer J. et al. *NMR Biomed* 1998;11:19-31.

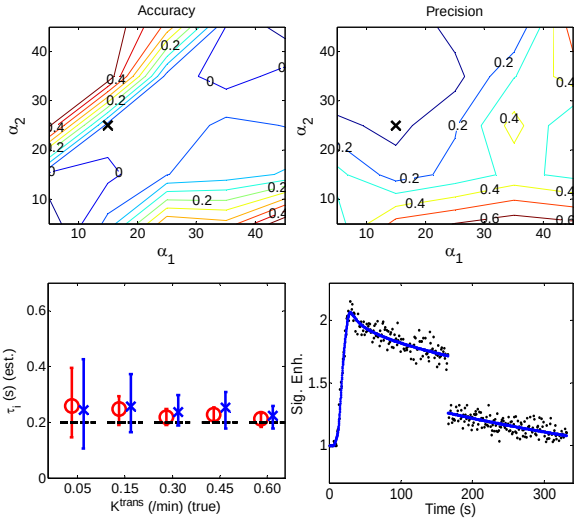

Figure 1: Numerical simulation study with different pairs of two flip angles. (a) accuracy of τ_i estimation (estimated - true) (b) precision of τ_i estimation (inter quartile range, 25%-tile - 75%-tile, of estimated τ_i) Black crosses indicates the choice of flip angles (α_1=15˚ and α_2=25˚) used for the preclinical in vivo study. (c) Uncertainty in τ_i estimation depending on flip angles; single flip angle method (blue crosses) and two flip angle method (red circles). (d) example of simulation data with model fit.

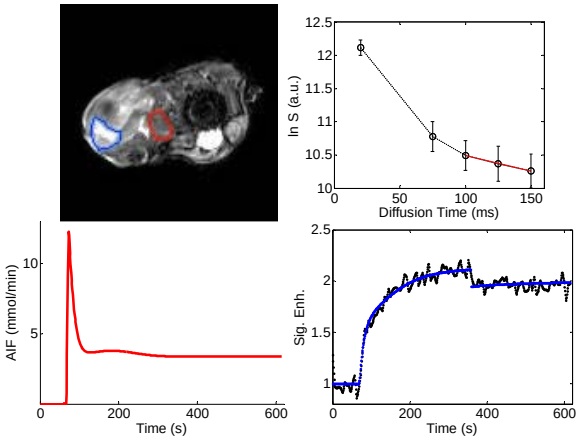

Figure 2: Representative example of mouse MRI data. (a) Examples of regions of interest: muscle (red) and tumor ROI (blue), (b) Constant gradient (cg) DWI experiment data from the ROI of the tumor shown in (a). Red line is a linear fit to the data with diffusion times longer than 75 ms, (c) arterial input function generated from muscle ROI using reference tissue method, (d) DCE-MRI data for the tumor shown in (a) and model fit (blue line).

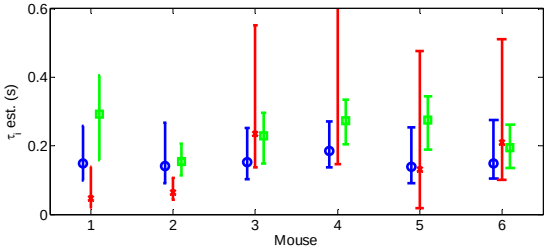

Figure 3: Comparison of estimated intracellular water life time (τ_i) measured by using different methods; cg-DWI (blue), DCE-MRI with one flip angle (red) and two flip angles (green). Medians and inter-quartile range are shown.