Intracellular water lifetime measured by diffusion weighted and dynamic contrast enhanced MRI

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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. However, extracting physiologically relevant parameters from DCE-MRI data is still a challenging problem. Gd-DTPA particles do not enter the intracellular space. In MRI, the contrast agent concentration is indirectly measured by its effect on water molecules which can access all tissue compartments. It has been reported earlier that water exchange between interstitium and intracellular space may not be fast enough to be ignored in DCE-MRI [3]. Cross-validation of such effect in DCE-MRI is not trivial. Exchange of intracellular water affects diffusion measurement. It has also been reported that τ_i can be measured by constant gradient diffusion weighted imaging (DWI) experiment [4]. Thus, the objective of this study was to compare intracellular water lifetimes measured by in vivo DCE-MRI and DWI experiment in a mouse tumor model.

Materials and Methods:

Six- to eight-wk-old BALB/c mice (n = 6) were given a subcutaneous injection in the right flank with 1 x 10^5 4T1 mouse mammary tumor cells suspended in 0.1 ml of PBS on day 0. Five mice were scanned on day 10~13 when the longest diameter of the tumor was about 10 mm. MRI was performed 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 32 ± 2 ºC during the scan. A T2-weighted rapid acquisition with relaxation enhancement (RARE) sequence was used to image the entire tumor (TR = 2s, TE = 35ms, FA=180º, res = 0.18 x 0.18 x 1.5 mm, 10 slices), and to select one slice near the tumor center.

DWI experiment was conducted with a stimulated echo diffusion weighted sequence with TR =2 s, TE = 32.7 ms, image matrix =64 x 48, 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, 30, 50, 75, 100, 150, and 200 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].

For DCE-MRI, a 3D FLASH sequence was used to minimize the flow effect (TR = 13.4 ms, TE = 3.0 ms, flip angle = 50º, image matrix = 64 x 36 x 8, resolution = 0.7 x 0.7 x 1.5 mm, temporal resolution = 3.85 s). This sequence was run to acquire two hundred single average 3D images for 12.8 min. 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 15 pre-contrast images (~ 1 min).

Arterial input function (AIF) was obtained from a reference region (RR) in the muscle [5]. K^{trans} and V_e of RR were assumed to be 0.05 min^{-1} and 0.11, respectively. DCE-MRI data was analyzed using the adiabatic approximation of tissue homogeneity model with water exchange (ATH-WX) model [6, 7] which provides the estimates of permeability-surface area product (PS), blood flow (F), mean transit time (T), extravascular-extracellular volume fraction (v_e), vascular water lifetime (τ_b) and τ_i. Transfer rate, K^{trans}, was calculated from the estimated PS and F.

Results and Discussion:

Figure 1 shows an example of DWI experiment. As shown in Fig.1c, there were two phases in the signal decay; fast with diffusion times shorter than 75 ms and slow with diffusion times longer than 75 ms. The red line in Fig.1c is a linear regression line of which slop is - 0.01, corresponding to intracellular water lifetime of 100 ms. Fig.1b shows the result of voxelwise analysis. The median (inter-quartile range) of τ_i from DWI was 99 (89 – 112) ms.

Figure 2 shows the result of DCE-MRI experiment for the same tumor shown in Fig.1. Heterogeneous distribution of ATH-WX parameters well represents the complex tumor microcirculation environment. The intracellular water lifetime τ_i estimated from DCE-MRI was 272 (133 – 574) ms. Figure 3 shows comparison of τ_i estimated from both modalities. Although the distribution of τ_i estimated from DCE is much broader than that of DWI, it has the mode very close to that of DWI.

This is the first *in vivo* imaging study, to our best knowledge, to measure τ_i using both DWI and DCE-MRI and to report a good agreement between their estimates. Our results substantiate that DCE-MRI using a proper pharmacokinetic model can provide reasonably accurate estimates of intracellular water lifetime. Intracellular water lifetime from DCE-MRI, together with volume fractions of intracellular and interstitial compartments, can provide useful information regarding tumor cell viability.

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] Landis C.S. et al., *MRM* 1999;42:467 – 478. [4] Pfeuffer J. et al., *NMR Biomed* 1998;11:19-31. [5] Yankeelov et al. J MRI, 2006;24(5):1140-7. [6] St. Lawrence K.S. and Lee T.Y., *J Cereb Blood Flow Metab*, 1998;18:1365-1377. [7] Zhang and Kim, ISMRM2010.

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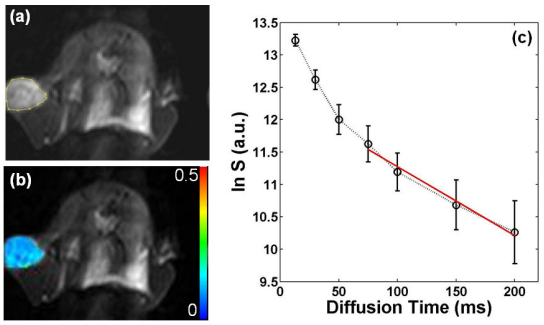

Figure 1: (a) Diffusion weighted image of 4T1 tumor. (b) Pixel map of intracellular water lifetime. (c) Constant gradient (cg)-experiment data from the ROI of the tumor shown in (a). Red line is a linear fit to the data with diffusion times bigger than 75 ms.

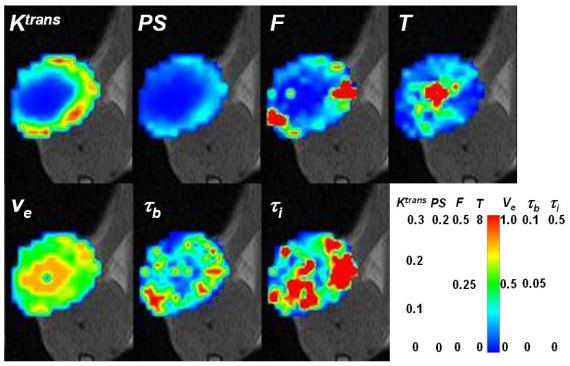

Figure 2: ATH-WX model parameters estimated from the same tumor shown in Fig.1.

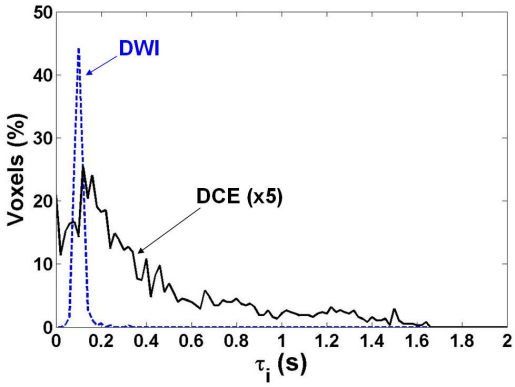

Figure 3: Comparison of τi histograms from tumour lesion measured by both DCE-MRI and DWI methods. The histogram of DCE-MRI was multiplied by 5 for clarity in presentation.