Exchange Resolved Measurements of Extra-cellular Volume in a Graded Muscle Edema Model

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Introduction

Two compartment models are widely used to describe NMR relaxation in tissue and typically involve an assumption of either fast or slow inter-compartmental water exchange rates. In many cases, however, inter-compartmental water exchange is intermediate and significantly alters the observed ^{1}H relaxation. For example, previous studies of injured skeletal muscle have shown two T_2 relaxation components, which have been attributed to intra- and extra-cellular water under the assumption of slow water exchange [1,2]. Without this assumption, inverting the transverse relaxation decay in a two-pool model with exchange is ill posed without knowledge of at least one of the intrinsic model parameters. Measuring T_2 with and without a compartment-specific contrast agent can provide such knowledge and allow complete inversion of the two-pool model. This work presents an approach for such measurements, experimental studies in injured rat skeletal muscle, and validation of the inversion through measurement of the extra-cellular volume fraction with SPECT.

Methods

Female Sprague-Dawley rats (n=8, 232g-256g) received a 0.1ml hindlimb injection of λ-carrageenan at one of four concentrations (0.125, 0.25, 0.5, or 1.0 % w/v) to induce inflammation. Six hours later, animals were imaged at 9.4T with a single slice multiple spin-echo sequence (30 echoes evenly spaced at 10 ms plus 6 echoes at 50 ms spacing, 15s TR, 2 NEX) and again 20 minutes after the administration of 200μL Gd-DTPA (0.4 mmol/kg). The echo magnitudes from an ROI in the region of injury were fitted to a bi-exponential function to extract values of two observed relaxation rates, R_a' and R_b' and observed volume fractions, f_a' and f_b'. (N.B. the superscript $'$ distinguishes the observed value from the intrinsic model value.) Because the mean relaxation rate is independent of exchange, the change in mean relaxation rate due to contrast agent injection is simply

$$\Delta R_m = R_{m+} - R_m = f'_{a+}R'_{a+} + f'_{b+}R'_{b+} - f'_aR'_a - f'_bR'_b = f_b r_b [CA],$$

and the change in the rate difference is

$$\Delta R_s = R'_{a+} + R'_{b+} - R'_a - R'_b = r_b [CA],$$

where [CA] is the contrast agent concentration, r_b is the relaxivity of the agent in compartment b, and the '$_+$' subscript indicates a post-contrast measurement. From here, the intrinsic extra-cellular volume fraction was estimated as $\hat{f}_{b,MRI} = \Delta R_m / \Delta R_s$,

which was then used to estimate all intrinsic model parameters from known solutions to the two-pool model with exchange [3].

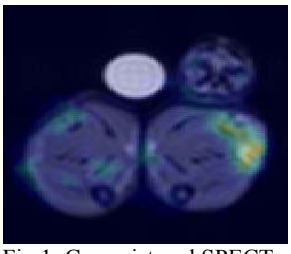

Fig 1. Co-registered SPECT-MR image.

Immediately following MRI, the renal vessels of the animal were ligated to create equilibrium between the vascular and interstitial space for subsequent SPECT experiments. ^{111}In-DTPA (~1mCi) was injected and ~20-30 minutes later, SPECT images of the hindlimb and a blood sample were collected. The ^{111}In SPECT image of the rat leg was co-registered to the MRI image (Fig 1), and the signal intensity was equated to an estimate of the extra-cellular volume fraction, $\hat{f}_{b,SPECT}$ using the ^{111}In image of the blood sample and known sample/voxel volumes.

Results

Edematous regions of muscle exhibited multi-exponential T_2 with two dominant components, and the long-lived signal fraction (f_b') only modestly agreed (R^2 = 0.43, intercept 0.17) with the extra-cellular volume fraction as measured by SPECT (Fig 2a). Using T_2 measurements before and after the Gd-DTPA injection, however, resulted in estimates of the extra-cellular volume fraction ($\hat{f}_{b,MRI}$) that more closely agreed with the SPECT-based measures (R^2=0.71, intercept = 0.05, Fig 2b).

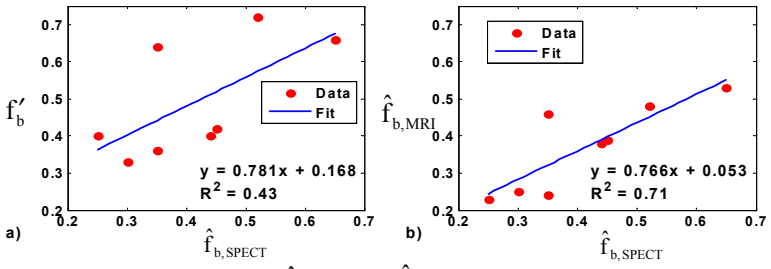

Fig 2. a) f_b' (from T_2) vs. $\hat{f}_{b,SPECT}$ b) $\hat{f}_{b,MRI}$ (from two-pool inversion) vs. $\hat{f}_{b,SPECT}$.

Conclusion

A two-pool model of water proton transverse relaxation in injured muscle, including inter-compartmental exchange was inverted using a simple two-measurement method (before and after Gd-DTPA) that did not require knowledge of contrast agent concentration or relaxivity. Measurements were validated by comparison to extra-cellular volume fraction measurements made using ^{111}In-DTPA SPECT images, which were insensitive to inter-compartmental water exchange.

References

1. Z Ababneh et al. MRM (2005) 54, 524. 2. RH Fan and MD Does. NMR Biomed (2008). 21, 566. 3. JR Zimmerman and WE Brittin. J Phys Chem (1957) 61,1328.