Measuring intra- and extra- cellular ADC in edematous skeletal muscle

R. H. Fan[1], and M. D. Does[1,2]

[1]Biomedical Engineering, Vanderbilt University, Nashville, TN, United States, [2]Radiology and Radiological Sciences, Vanderbilt University, Nashville, TN, United States

Introduction:

Diffusion tensor imaging (DTI) of skeletal muscle has been shown to reflect tissue damage due to ischemia (1) or traumatic injury (2). In both studies, decreases in fractional anisotropy (FA) and increases in the apparent diffusion coefficient (ADC) were found in injured muscle tissue. These results are consistent with a membrane damage resulting in a less ordered and less restricted tissue, and are consistent with diffusion measurements in injured neural tissue (3), but further micro-anatomical details are not clear. Galbán et al. proposed that the second and third eigenvalues of the diffusion tensor correspond, respectively, to inter- and intra-cellular water diffusing perpendicular to the long axis of the of normal muscle fibers (4), but it is not clear how this relates to the microanatomy of injured muscle. In another study, multi-exponential decompositions of T_2 and diffusion measurements were investigated in edematous muscle as a means to relate T_2s and ADCs to specific anatomical compartments (5); however, the results, much like similar studies in neural tissue, indicated that while multiexponential T_2 may resolve signal from different anatomical compartments, similar measures of diffusion do not. Compartmentally-specific ADC measurements of water in neural tissues have been made by several investigators by integrating diffusion- and T_2-weighting (6-8), and in this study a similar approach has been used to probe the compartmental basis of water diffusion in edematous muscle.

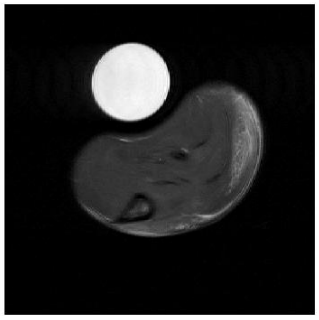

Figure 1. High resolution FSE image Rat Hind Limb with edema:

Methods:

Six male Sprague-Dawley rats, average mass of 358g, range 327-427g, were anesthetized with 2% isoflurane and given a 0.1mL 1% w/v subcutaneous injection of λ-carrageenan in either the right or left hind limb above the calf to induce edema. At least 6 hours was allowed for the λ-carrageenan induced edema to reach a pseudo steady-state level prior to imaging. All imaging studies were performed on at 300 MHz on a 7 T 16-cm animal MRI system using a 25 mm Litz coil. Regions of edematous muscle were identified with fast spin echo imaging, Fig 1, then a diffusion-weighted multi-spin-echo (DW-ME) imaging sequence was used for the integrated ADC-T_2 measurements. For each diffusion weighting, a total of 38 echoes were acquired. Cross term correction was achieved using a positive/negative diffusion gradient scheme. Imaging parameters were TR = 2000ms, first echo = 21ms, inter-echo spacing = 10ms, Δ = 12ms, δ = 6ms, FOV = 35x35mm, matrix; 64x64, spectral width = 25 kHz, NEX = 2. Diffusion weighting was applied along the read, phase, and slice directions, at equally spaced b-values 0-500s/mm^2, resulting in a total of 38 echoes from each of 18 different diffusion-weightings. Although the full diffusion tensor was not measured with multiple echoes and b-values, a more rapid, standard DTI protocol was used to confirm that the slice orientation was closely aligned with the direction of greater water diffusion (average difference was 9° ± 5°).

Three ROI's were selected (phantom, normal muscle, and edematous muscle) from which echo magnitudes were extracted and fitted with a one- or two-component model

$$S = S_o e^{(-te/T_2)} e^{(-bD)} \text{ or } S = S_a e^{(-te/T_{2a})} e^{(-bD_a)} + S_b e^{(-te/T_{2b})} e^{(-bD_b)}, \quad [1]$$

where S is the echo magnitude and subscripts a and b indicate two different signal components. In a two-compartment, slow-exchange model, these signal components can be directly ascribed to water from two micro-anatomical compartments.

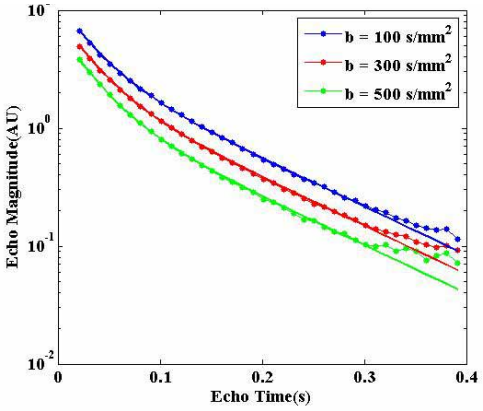

Figure 2. Plot of acquire data, solid dots, and modeled data, lines, according to equation [1].

Results and Discussion

The resultant edema from λ-carrageenan injection is shown in the upper right region of the rat hind leg in Fig 1. Typical echo magnitudes (solid dots) from the DW-ME acquisitions are shown in Fig 2 along with predicted values from the fit to Eq [1]. For normal muscle, the data were best described by a single-component model with T_2 = 24 ± 0.6 ms. In edematous muscle, a two-compartment model was necessary with T_{2a} = 33.4 ± 5.3 ms and T_{2b} = 126.2 ± 19 ms, and relative fractions of S_a = 0.60 ± 0.1 and S_b = 0.40 ± 0.1. Table 1 shows the full list of fitted water diffusion parameters, plus the rotationally invariant ADC (mean of D in read, phase, and slice directions), and pseudo-fractional anisotropy, α, which was calculated with the simplification that slice, read, and phase directions correspond to the directions of the three eigenvectors of a full diffusion tensor.

These data indicate that echo time is an important factor in assessing and comparing DTI measurements from injured muscle: longer echo times will result in greater ADCs and lower FAs. In the context of a two compartment interpretation, the data indicate that the extra-cellular water in edematous tissue is responsible for the increased ADC, and that this water shows very little diffusional anisotropy. If one assumes that the edema causes changes only in the extra-cellular space, then the short-lived water (T_2 = 33 ms) in the edematous tissue should compare closely with the intra-cellular water in normal tissue. This would indicate that normal extra-cellular water is responsible for almost half the observed FA. However, this interpretation would also require that, in normal muscle, the extra-cellular water fraction be at least 18 % (assuming unrestricted water diffusion in the slice direction), which is large compared to other estimates (13 % (9)). Further studies are necessary to test/refine the compartmental interpretation, but the integrated ADC-T2 measure offers promise to provide more specific information on the anatomical basis of muscle injuries, observed with MRI.

	D_{read} (μm^2/ms)	D_{phase} (μm^2/ms)	D_{slice} (μm^2/ms)	ADC (μm^2/ms)	α
Normal Muscle (T_2 = 24 ms)	1.22 ± 0.10	1.31 ± 0.12	1.81 ± 0.09	1.45	0.22
Edematous Muscle (T_2 = 33 ms)	1.15 ± 0.16	1.19 ± 0.24	1.44 ± 0.17	1.26	0.12
Edematous Muscle (T_2 = 126 ms)	2.11 ± 0.20	2.07 ± 0.22	2.32 ± 0.14	2.17	0.06

Table 1. Measured diffusion coefficients for normal and two components of edematous muscle.

References

1. Heemskerk et al. MRM 2006, 2. Zaraiskaya et al. JMRI 2006, 3. Beaulieu et al. MRM 1996, 4. Galbán et al. Eur JAP 2004, 5. Ababneh *et al* MRM 2005, 6. van Dusschoten et al. MRM 1996, 7. Does and Gore MRM 2000, 8. Travis and Does, MRM 2005, 9. Cieslar *et al.* AJP 1998.

Acknowledgements

The authors would like to acknowledge financial support from the NIH, Grant #EB001744.