Time-dependent diffusion in skeletal muscle of normal controls and chronic exertional compartment syndrome patients

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Target Audience: Scientists and clinicians working in quantitative imaging of skeletal muscle pathology, particularly chronic exertional compartment syndrome.

Purpose: Diffusion tensor imaging (DTI) provides quantitative markers of tissue microstructure and can be used as a probe in the evaluation of skeletal muscle disease [1-4]. Furthermore, controlled variation of the diffusion time, and corresponding modulation of the degree of restricted diffusion, can provide enhanced specificity with proper modeling as has been shown in several biological tissues [5-8]. In chronic exertional compartment syndrome (CECS) [9-11], muscle compartments retain fluid following exercise leading to elevated pressure, reduced perfusion, pain, and ischemia. Since current standard diagnostic and therapeutic tools including intracompartmental pressure measurements and fasciotomy are invasive and inconsistently successful, noninvasive MRI markers are attractive alternatives. T2 signal increase is a known marker of post-exercise muscular edema [12-14], and recently long-time DTI [15] showed that diffusion anisotropy changes also accompany CECS. This study employs time-dependent diffusion (D(t)) acquisition and the recently proposed random permeable barrier model (RPBM) [6,7] to shed further light on the microstructural features of the CECS pathophysiology.

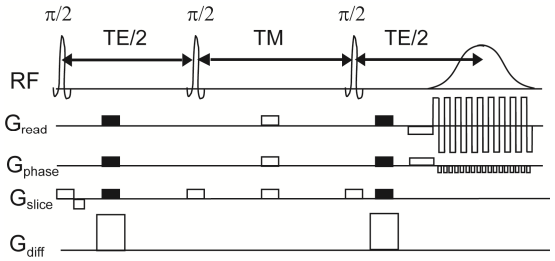

Figure 1: Stimulated echo diffusion-weighted MRI sequence with EPI readout. Dark boxes represent spoiler gradients activated only for b=0 images.

Methods: Seven patients with clinical suspicion of CECS and eight healthy volunteers underwent MR imaging of the lower leg in a study approved by the local institutional review board (IRB). Images were collected in a wide-bore Siemens Verio 3 T scanner with a unilateral 15-channel knee coil. DTI results were obtained both at rest and after 10 minutes of maximal treadmill exertion, using a stimulated echo diffusion sequence [16](Fig. 1) with echo-planar imaging readout (TR / TE = 12400 / 31-42, 64 x 64 x 10 matrix, 3 x 3 x 5 mm resolution, 6 directions, b = 0, 500 s/mm^2, 3 avgs.) and adjustable mixing time TM. Four different effective diffusion times T_d = TM + TE/2 of 30, 70, 520, and 1020 ms were acquired by varying TM. Two patients had T_d of 170 ms rather than 70 ms. DTI data were processed offline (Igor Pro, Wavemetics) to generate maps of MD, FA, and diffusion eigenvalues (λ_1,λ_2,λ_3), incorporating encoding matrices (b-matrices) provided by the vendor software including the effects of all imaging, spoiler, and diffusion gradients [17-19]. Regions of interest (ROI) were manually segmented to estimate diffusion metrics in anterior tibialis (AT), extensor digitorum longus (EDL), posterior tibialis (PT), peroneus longus (PL), soleus (SOL), gastrocnemius lateralis (GL) and gastrocnemius medialis (GM). From these data, radial diffusivity (λ_{rad}) was calculated (λ_{rad} = (λ_2 + λ_3)/2) for each T_d and muscle compartment and its time dependence was fitted to RPBM [6,7] to extract free diffusivity D_0, fiber diameter a, and permeability κ. Diameters were compared with values from quantitative analysis of autopsy specimens [20]. Response factors (post- to pre-exercise ratios) were compared between volunteers and patients for each parameter with two-sided t-tests (SPSS).

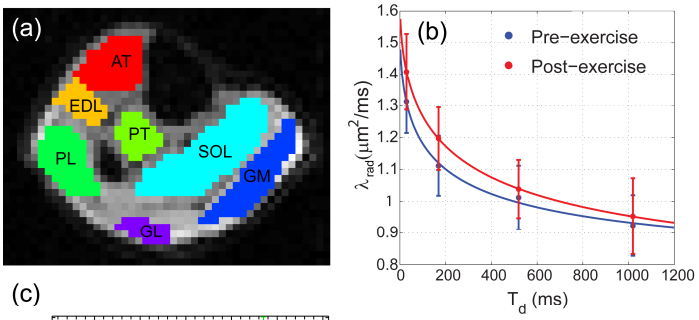

Figure 2: (a) Regions of interest (ROI) drawn on a DWI in different muscle compartments. (b) Time-dependence and model fits of radial diffusion in volunteer GM compartment. (c) Comparison of DTI-derived fiber sizes with literature values from quantitative autopsy data for both volunteers and patients pre and post-exercise.

Results: Figure 2a shows an example DWI with ROIs in each muscle compartment. Time-dependent radial diffusion values and model fits are shown in Figure 2b before and after exercise in a volunteer GM compartment. Model fitting was successful in all 15*7 = 105 muscle compartment fits except 3 GL cases which produced unphysical order of magnitude estimates and were excluded from the analysis. Figure 2c shows correlation of pre-and post-exercise fiber diameters in several muscle compartments with estimates from autopsy literature [20]. Figure 3a-3c shows the subject group comparison of response factors of each model parameter for all muscle compartments. Free diffusion D_0 increases by 5% in volunteers and 10% in CECS subjects. Fiber diameter (a) increases by 20% on average in volunteers but changes negligibly in patients. Permeability κ does not change in volunteers but increases by 60% in patients. All parameters showed significant ($p<0.05$) differences between group response factors.

Discussion: Fiber diameter estimates for individual compartments are in good agreement with estimates from autopsy studies, as found previously [7]. Figure 3d shows hypothesized changes consistent with these observations. In volunteers, significant fiber dilation occurs but fiber integrity, i.e. permeability, is largely unchanged, while in CECS patients, trapped interfascicular muscular edema may increase free diffusivity and apparent permeability, while dilation may be prohibited by the elevated intracompartmental pressure. This differentation may help guide treatments that either relieve pressure directly (fasciotomy) or increase fiber integrity to modulate exchange. This study is limited by low subject number and lack of external validation (e.g. pressure measurements) but is a compelling example of enhanced specificity provided by time-dependent diffusion analysis and biophysical modeling [6].

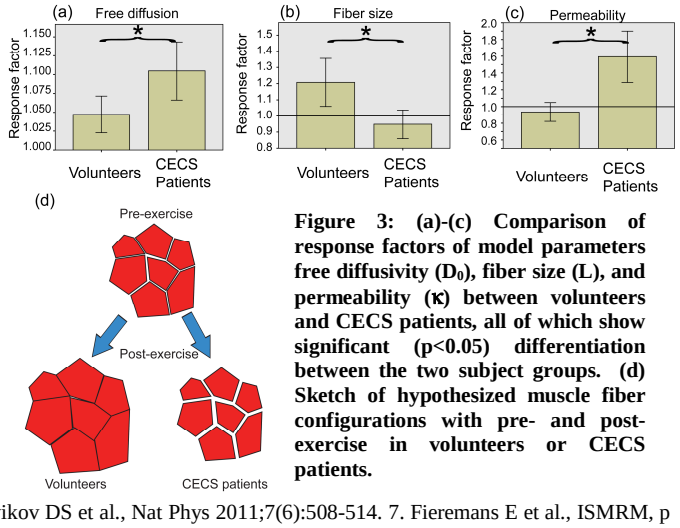

Figure 3: (a)-(c) Comparison of response factors of model parameters free diffusivity (D_0), fiber size (L), and permeability (κ) between volunteers and CECS patients, all of which show significant ($p<0.05$) differentiation between the two subject groups. (d) Sketch of hypothesized muscle fiber configurations with pre- and post-exercise in volunteers or CECS patients.

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