Observation of muscle fiber diameter increase with exercise using time-dependent diffusion

Els Fieremans[1], Gregory Lemberskiy[1], Jens H Jensen[2], and Dmitry S Novikov[1]
[1]Center for Biomedical Imaging, Department of Radiology, NYU School of Medicine, New York, NY, United States, [2]Center for Biomedical Imaging, Department of Radiology and Radiological Science, Medical University of South Carolina, Charleston, SC, United States

INTRODUCTION: The dependence of the diffusion coefficient in biological tissues on the diffusion time is a hallmark of tissue microstructure. Recently, a random permeable barriers model (RPBM) was suggested to harness this time-dependence in order to quantify cell size and membrane permeability [1]. As applied to muscle fibers [2], assuming the cell membrane of a myofiber (sarcolemma) as the predominant restriction to water motion, this method [1,2] allows estimating the free diffusion coefficient D_0, myofiber membrane permeability κ, and mean muscle fiber diameter a from measuring time-dependent diffusion in the direction transverse to the fibers. *Purpose:* To study changes in muscular microstructure in a healthy volunteer over the course of a 12-week weight lifting program, whereby we hypothesized that muscle fiber diameters in targeted regions would increase with training. *Target audience*: MR physicists and clinicians interested in clinically feasible quantitative biomarkers of tissue microstructure.

METHODS: A 35 y/o right-handed male healthy control was followed over the course of a 12-week weight-lifting program during which his body mass index decreased from 28.8 down to 27. MRI was performed of the left calf muscle on week 0, 4, 8, 10 and 12 using a 3T wide-bore Siemens Verio system with an 8-channel knee coil. DWI images were acquired for $b = 0$, and along 6 gradients directions for $b = 500$ s/mm^2. Stimulated echo diffusion preparations for 9 different diffusion times t from 31 ms up to 1518 ms were obtained by varying mixing time. Other imaging parameters were: 3 averages, TR > 7.4 s, TE = 42 ms, matrix = 64 x 64, FOV = 190 x 190 mm^2, thickness = 5 mm. Total scan time was 50 min for each session. DTI parametric maps of the diffusion eigenvalues (λ_1,λ_2,λ_3) were calculated for all diffusion times using in-house developed software in Matlab. The corrected b-matrix, as provided in the vendor sequence (WIP511), was used to include the contributions of both applied diffusion gradients and imaging gradients. The accuracy of the acquisition was verified by testing the protocol on several liquids in which the diffusion coefficient was shown to be independent and isotropic over the range of employed diffusion times. A systematic vibration artifact was observed in 10% of acquired DWI images, and filtered out before averaging [3]. Regions of interest (ROIs) were manually outlined on T_2-weighted anatomical images (Fig. 1(a)) to study the time-dependent diffusion in the Anterior Tibialis (AT), Extensor Digitorum Longus (EDL), Gastrocnemius Medialis (GM), Gastrocnemius Lateralis (GL), Peroneous Longus (PL), Posterior Tibialis (PT) and Soleus (SOL). For each ROI, the average value of the transverse diffusivity as a function of the diffusion time t, $D_\perp(t) = (\lambda_2 + \lambda_3)/2$, was used to fit to the RPBM [1] to extract free the diffusivity D_0, fiber diameter a, and membrane permeability κ. The change of each model parameter with the training period was then assessed by the Pearson correlation coefficient.

RESULTS: For all muscle groups and scan times, the largest eigenvalue λ_1 initially decreases by on average 14% ± 4% and then levels off for t > 100ms, whereas the transverse diffusivity $D_\perp$ decreased by on average 40% ± 5% over the observed time range, as illustrated in Fig. 1(b) for the scan at week 0. $D_\perp(t)$ agrees well with the RPBM [1] in all data sets (R^2-values ≥ 0.98) The fitted model parameters in each muscle group did not significantly correlate with training period, except for the fiber diameter in the GM ($\rho = 0.84$, $p \leq 0.05$). The fitted values for the fiber diameter a, are plotted in Fig. 1(c) as a function of training period, and values for membrane permeability κ and free diffusivity D_0 in each muscle group averaged over all scan times are listed in Table 1. Fiber diameters are compared to histology values derived from literature [4] in Fig. 1(d).

DISCUSSION: The RPBM [1] yields realistic values for the mean muscle fiber diameter and membrane permeability [4,5]. The estimated fiber diameters for different muscle groups are consistent with human myofiber histology, Fig. 1(c): Specifically, the smallest fibers are found in the EDL and largest in SOL and GM, which is in agreement with histological findings [4]. Additional as expected, *a significant increase in fiber diameter with training is found in the GM*. As the GM is indeed preferentially targeted by weightlifting exercises, this experiment serves as an *in vivo* validation of the RPBM.

CONCLUSION: We demonstrated the feasibility of the *in vivo* RPBM method [1,2] for quantifying muscle fiber diameter and membrane permeability from time-dependent diffusion measurements, as well as its sensitivity to microstructural changes. This work illustrates the potential for clinical assessment of muscular pathologies, e.g. Duchenne muscular dystrophy, requiring the distinction between cell morphology (e.g. mean diameter) and integrity (permeability).

TABLE 1: Fitted values (mean ± S.D. over all scan times) for the membrane permeability κ and free diffusivity D_0

ROI	κ [μm/ms]	D_0 [μm^2/ms]
AT	0.026 ± 0.005	1.82± 0.019
EDL	0.024± 0.003	1.87± 0.017
GL	0.038± 0.003	1.87± 0.015
GM	0.033± 0.004	1.76± 0.020
PL	0.029± 0.005	1.82± 0.016
PT	0.024± 0.005	1.86± 0.023
SOL	0.034± 0.004	1.77± 0.022

REFERENCES: [1] Novikov et al. Nat Phys **7**:508,2011; [2] Fieremans et al, ISMRM 2011, 1153; [3] Lemberskiy et al., submitted; [4] Polgar et al. J Neurol Sc **19**:307, 1973; [5] Landis et al. MRM **42**:467,1999;

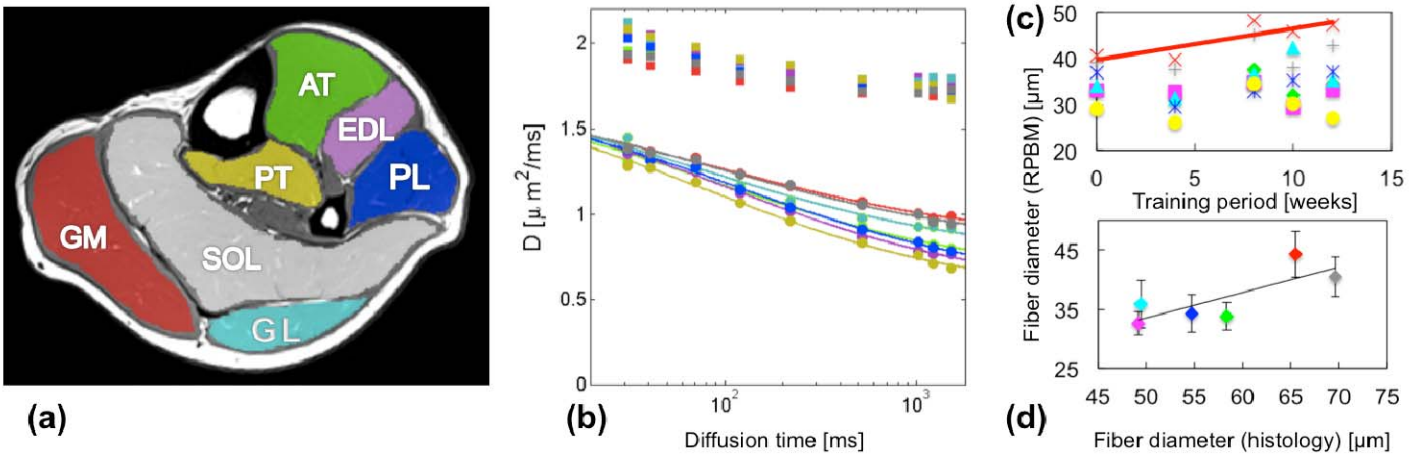

FIGURE 1: **(a)** Anatomical T_{2w}-MRI image showing the muscle ROIs; **(b-d)** the colors of the data points and fitted curves match the color of the ROIs in (a); **(b)** Example of the time-dependence of the parallel and transverse diffusivity, the latter decreases with time and is fitted to the permeable barriers model [1], resulting in fitted values for the free diffusivity D_0, fiber size L, and membrane permeability κ ((c-d) and Table 1); **(c)** Changes of the fiber size with training period, a significant increase with training time is only observed for the GM ($\rho = 0.84$, $p \leq 0.05$); **(d)** Comparison of the fitted fiber sizes with histology values from literature [3]. The error bars represent variation over the different scan times.