A Diffusion Tensor Imaging Analysis of Gender Differences in Water Diffusivity within Human Skeletal Muscle

C. J. Galban[1], S. Maderwald[1], K. Uffmann[1], M. E. Ladd[1]

[1]University Hospital of Essen, Essen, Germany

Abstract: Diffusion tensor imaging was used to determine if gender differences exist in water diffusivity within the calf muscles. The eigenvalues, trace of the diffusion tensor, and two anisotropic parameters were calculated and compared. A mathematical model was also derived to determine if differences in muscle fiber volume per total volume (muscle fiber volume fraction) could account for the differences seen between the sexes. This study concluded that gender differences do exist, and that variations in muscle fiber volume fraction could play a significant role in the diffusive properties of water in skeletal muscle.

Introduction: Diffusion tensor imaging (DTI) has been used to study structural changes in various living tissues. Presently, most of the work involving DTI has been devoted to brain research, such as 3D visualization of fiber tracks and monitoring diffusive properties of water in the presence of various diseases. DTI has also been employed, although to a lesser extent, for studying skeletal muscle physiology, through the use of the apparent diffusion coefficient, and structure, though the use of the principle eigenvector of the diffusion tensor. Recent work by our group has shown that diffusive properties of water differ between adjacent muscles, and that these differences may be attributed to the overall function of the muscle[1]. The present study expands on the previous research by demonstrating that gender differences also exist and that these differences may be related to differences in muscle fiber volume.

Methods and Materials: *Subjects:* Twenty-four untrained subjects, twelve males and twelve females, volunteered to participate in this study.

MRI Experiment: All MRI scans were performed with the subjects lying supine, feet first in a 1.5 T full-body scanner (Siemens Sonata, Erlangen, Germany). A standard extremity coil was used to scan the calf region of each subject's left leg. T_2-weighted images were acquired using a single-shot spin-echo EPI sequence with the following parameters: repetition time/echo time = 2000/95 ms, field of view (FOV) = 18x13.5 cm, matrix size = 128x96, slice thickness = 6 mm, and number of averages = 16. Diffusion gradients were applied along six directions with a b value of 400 s-mm^{-2}. In addition, a T_2-weighted image, used for calculating the diffusion tensor, was acquired with a b value of 0 s-mm^{-2}. A single slice was acquired approximately 10 cm below the tibial head. To specify the regions of interest (ROI) for the individual muscles, a high contrast T_1-weighted FLASH sequence was used with the following parameters.

Diffusion Tensor Imaging: The images were processed and the diffusion tensor was calculated for each pixel as described in Basser et al., [2]. ROI's were specified using the individual FLASH image for seven different muscles as shown in Figure 3 in Galban et al.,[1]. The muscles analyzed were the soleus (SOL), lateral gastrocnemius (LG), medial gastrocnemius (MG), posterior tibialis (PT), anterior tibialis (AT), extensor digitorum longus (EDL), and the peroneus longus (PL). For each ROI, six calculations were made: three eigenvalues of the diffusion tensor ($\lambda_1 \geq \lambda_2 \geq \lambda_3$), the trace of the diffusion tensor Tr(**D**), the ellipsoid eccentricity *e* [3], and the fractional anisotropy FA [4]. Statistical significance was assessed using an ANOVA at P<0.05. Data are shown as mean ± SEM.

Theoretical Model: The mathematical model was based on the derivation of the effective diffusion coefficient using the volume averaging method (VAM). The effective diffusion tensor for a cellular medium, as described by Ochoa et al., [5], was used to represent diffusive transport through skeletal muscle. Assumptions were employed to simplify the expression for the diffusion tensor. Most important were the assumptions of a cylindrical geometry and that water diffusion parallel and perpendicular to muscle fibers can be represented by two separate diffusion coefficients. The derived effective diffusion tensor can be written as

$$\mathbf{D} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix} = \begin{bmatrix} \varepsilon_\alpha D_\alpha^{=} + \varepsilon_\beta D_\beta & 0 & 0 \\ 0 & \varepsilon_\alpha D_\alpha^{\perp} + \varepsilon_\beta D_\beta & 0 \\ 0 & 0 & \varepsilon_\alpha D_\alpha^{\perp} + \varepsilon_\beta D_\beta \end{bmatrix} \quad (1)$$

where α is the muscle fiber phase, β is the interstitial phase between the fibers, ε_i is the volume fraction in phase i (ε_β=1-ε_α), D_β is the diffusion coefficient in the isotropic β phase, $D_\alpha^{=}$ is the diffusion coefficient in the α phase parallel to the myofibrils, and $D_\alpha^{\perp}$ is the diffusion coefficient in the α phase perpendicular to the myofibrils. Eigenvalues (λ_{1S} and λ_{2S}) and the fractional anisotropy (FA_S) were acquired using Eq. (1) and fit to the experimental data using a χ^2 test.

Results: Statistical differences between the genders were seen for most of the muscles with respect to the eigenvalues and trace of the diffusion tensor (Figure 1). Only the large plantar flexor muscles, which consist of the soleus, lateral gastrocnemius, and medial gastrocnemius, showed statistical differences between the genders for the anisotropic parameters. The model, presented by Eq. (1), produced a good fit to the experimental data (Figure 2). Assuming a literature value of $D_\alpha^{=}$ 1.86 x10^{-3}mm^{2}s^{-1} and when using the experimental principle and second eigenvalues, the fit also generated values for D_β and $D_\alpha^{\perp}$ of 3.2x10^{-3}mm^{2}s^{-1} and 1.12 x10^{-3}mm^{2}s^{-1}, respectively, which are consistent with literature results[6, 7].

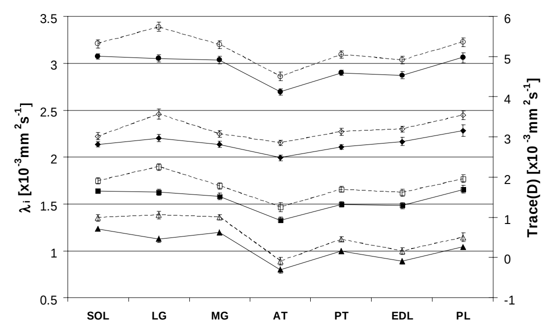

Figure 1: Line plots of λ_1 (◊), λ_2 (□), λ_3 (Δ) and TR(**D**) (○) for all muscles in both males (solid symbols) and females (hallow symbols). Along the horizontal axis are the individual muscles.

Discussion: The present study clearly demonstrates that differences in water diffusivity within skeletal muscle exist between healthy males and females. The large plantar flexor muscles showed the largest differences for most of the diffusive parameters. In contrast, the dorsiflexors produced minimal differences, especially in the anisotropic parameters. Based on the theoretical model, it has been shown in this study that these differences may be due to variations in muscle fiber volume fraction between both muscles and genders, i.e. larger muscle fiber volume fraction leads to higher FA and lower eigenvalues. By applying quantitative DTI for monitoring structural changes in muscle fibers, which are highly sensitive to disease, therapeutic drugs, and physical therapy, this technique may be used for determining muscle health and patient wellness.

References:

[1] Galban C.J., et al., Eur J Appl Physiol 2004;
[2] Basser P.J. and Pierpaoli C., Magn Reson Med 1998;39:928-34.
[3] Damon B.M., et al., Magn Reson Med 2002;48:97-104.
[4] Le Bihan D., et al., J Magn Reson Imaging 2001;13:534-46.
[5] Ochoa J.A., et al., Chem Engng Sci 1986;41:2999-3013.
[6] Simpson J.H. and Carr H.Y., Phys Rev 1958;111:1201-1202.
[7] Morvan D., et al., Magn Reson Med 1993;29:371-7.

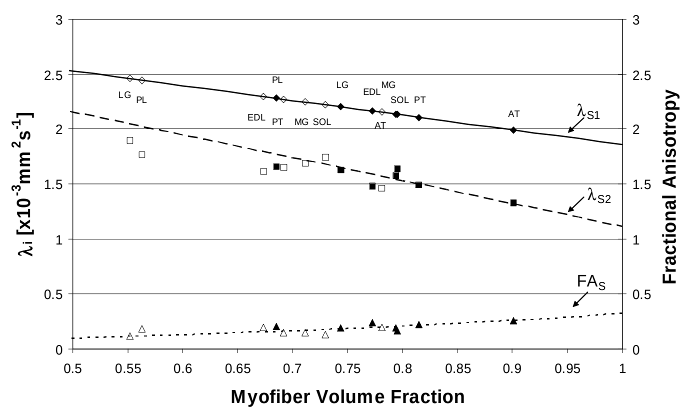

Figure 2: Plot of the simulated eigenvalues, experimental data, and FA_S. The experimental data from males (solid) and females (hallow) consisted of λ_1 (◊), λ_2 (□), and FA_S (Δ). Abbreviations for the muscles are above the corresponding λ_1 data points for males, and below for females. All data points for λ_2 and FA_S correspond to the muscle abbreviation immediately above that data point.