**Diffusion-weighted MRI of Skeletal and Cardiac Muscle**
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**Introduction: The Structural Basis of Anisotropic Diffusion in Striated Muscle**

The diffusion of water in striated muscles differs from that of free water in two ways. First, the apparent diffusion coefficient (ADC) is considerably reduced from that of free water. The second difference is its anisotropy, with a preferential diffusion along the fibers' long axes (1). The biological basis for these findings lies in the microstructure of striated muscle fibers. Striated muscle fibers are approximately circular in cross section with diameters of ~40-60 μm, but they can be several cm to tens of cm long. They also have a high content of longitudinally oriented proteins (~20% by weight) that are involved with either 1) producing force and length changes (the myofibrils) or 2) force transmission, maintenance of cell structure, and some intracellular signaling (the intermediate filaments). Finally, the cells' intracellular $Ca^{2+}$ store, the sarcoplasmic reticulum, is also longitudinally oriented. It is some combination of the finite permeability of the plasma and organelle membranes, the obstructive nature of the proteins themselves, and the mobility restriction associated with protein hydration that produce the reduced and anisotropic water diffusion. In regions of uniform fiber orientation, the transverse diffusivities depend strongly and seemingly monotonically on the diffusion time, reaching asymptotic values at times of ~500 ms (2); this suggests that the structure that is mainly responsible for transverse diffusion hindrance has a dimension of ~30 μm, or the cell radius.

When analyzed using a tensor model, water diffusion in skeletal muscle *in vivo* has first through third eigenvalues of $\lambda_1 \cong 2.2 \times 10^{-5}$ cm$^2$/s, $\lambda_2 \cong 1.6 \times 10^{-5}$ cm$^2$/s, and $\lambda_3 \cong 1.2 \times 10^{-5}$ cm$^2$/s, respectively (3); the corresponding values for cardiac muscle are $\lambda_1 \cong 0.9 \times 10^{-5}$ cm$^2$/s, $\lambda_2 \cong 0.6 \times 10^{-5}$ cm$^2$/s, and $\lambda_3 \cong 0.45 \times 10^{-5}$ cm$^2$/s (4). The predictable result from the Cleveland *et al.* study (1) – that the eigenvector ($\varepsilon_1$) corresponding to $\lambda_1$ lies along the long axis of the fiber – has been demonstrated in studies in both skeletal (5,6) and cardiac (7,8) muscle. Moreover, it has become increasingly clear that $\lambda_2$ and $\lambda_3$ do not represent the same cross-fiber diffusion process with corresponding eigenvectors ($\varepsilon_2$ and $\varepsilon_3$) that are mathematically constrained to be orthogonal to $\varepsilon_1$; instead, they have distinct structural bases. In cardiac muscle, a laminar structure exists that is characterized by stacked sheets (from apex to base) that are 4 fibers thick; $\varepsilon_2$ and $\varepsilon_3$ correspond to the sheet- and sheet-normal directions, respectively (8). In skeletal muscle, $\lambda_2$ and $\lambda_3$ appear to have distinct meanings as well; however the structural basis for these differences is not clear.

**DT-MRI in Studies of Striated Muscle Architecture and Mechanics**

Striated muscle is a classic example of a structure-function relationship. In skeletal muscle, peak muscle tension is proportional to the number of sarcomeres in parallel, while the velocity of unloaded shortening is proportional to the number of sarcomeres in series. Skeletal muscles can assume a number of designs (fusiform, pennate, multipennate, etc.) to optimize either the force or velocity potential of the muscle. Moreover, interactions such as between-fiber shear strain also influence the kinematic behavior of muscle fibers (9). While challenges such as low $T_2$, the presence of intramuscular fat, and difficult-to-shim volumes exist, we (5,10) and others (11,12) have demonstrated the feasibility of quantitative skeletal muscle fiber tractography *in vivo*. Van Donkelaar and colleagues have demonstrated the feasibility of forming finite element models of muscle mechanics on the basis of DTI data (6).

In cardiac muscle, DT-MRI-based descriptions of the orientation of $\varepsilon_1$ have agreed with histological observations, revealing alterations in the inclination angle that occur transmurally and alterations in the transverse angle that occur within a short-axis slice (7,8). Together, these observations describe a right-handed helix in the endocardium that transitions to a left-handed helix in the epicardium. Also, the mechanics of wall thickening and their alteration with heart tissue damage are of particular interest. Analysis of the eigenvector orientations alone (13) or in conjunction with strain measurements derived from phase-contrast MRI (14) at various points of the cardiac cycle have revealed how changes in fiber and laminar orientations contribute to the wall thickening process.

**DT-MRI in Studies of Striated Muscle Damage**

DT-MRI has emerged as a potentially important tool for detecting and following skeletal muscle damage. Following cardiac muscle infarction, the transverse diffusivity begins to decrease after ~60 min. (15), and ultimately the underlying fiber architecture becomes more disarrayed (16). During skeletal muscle ischemia, the ADC is reduced; this study also showed that ADC is increased following reperfusion, and that $\lambda_3$ in particular was correlated with damage scores and other histologically derived indices of muscle damage (17). Inflammatory muscle diseases are also characterized by elevated ADC values (18). The specific pathological processes (membrane disruption, intracellular swelling, extracellular edema, etc) involved in altering ADC in these models are not clear. However, it is likely that at least the edematous process is involved in elevating ADC, as λ-carrageenan injection in skeletal muscle causes the appearance of an additional $T_2$ and diffusion component, with the diffusion being larger and more isotropic than non-inflamed muscle (19).

**Conclusion**

DT-MRI is an important tool for structural analysis of striated muscle in states of health and disease, being sensitive to such important biological parameters as cell dimensions, edema, fiber orientation, and (in cardiac muscle) sheet orientation. These sensitivities permit applications including the study of fiber microstructure, muscle damage, and the investigation of the relationships between structure and function.

**References**

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