Clinical application of diffusion tensor magnetic resonance imaging in skeletal muscle

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Summary

Diffusion tensor magnetic resonance imaging (DTI) is increasingly applied in the detection and characterization of skeletal muscle. This promising technique has aroused much enthusiasm and generated high expectations, because it is able to provide some specific information of skeletal muscle that is not available from other imaging modalities. Compared with conventional MRI, DTI could reconstruct the trajectories of skeletal muscle fibers. It makes it possible to non-invasively detect several physiological values (diffusion values), like fractional anisotropy (FA) and apparent diffusion coefficient (ADC), which have a great association with the muscle physiology and pathology. Furthermore, other advantages of DTI are the capability of investigating the muscle biomechanics and also investigate the pathological condition of skeletal muscle. Finally, several challenges, which limit the wide application of DTI in skeletal muscle, were discussed. It is believed that this review may arouse in-depth studies on the clinical application of DTI in skeletal muscle in future.

Key words: skeletal muscle; MRI; diffusion tensor; fractional anisotropy; fiber tracking.

Introduction

Skeletal muscle is an important tissue structure existing in human body, and a quantity researches have engaged in studying the architectural structure and physiological function of the peripheral skeletal muscle (1-7). At present, many investigations studying muscle relied on invasive muscle biopsy method, which has a great limitation in wide application clinically (8). Thus, there is a great request to develop a non-invasive and subject-specific technique, in order to analyze morphological and functional data of a whole skeletal muscle (9).

Magnetic resonance imaging (MRI) is a non-invasive and favorable imaging method to provide a wealth of information on the morphology and function of skeletal muscle (10-12). Compared to the traditional two-dimensional MRI methods, a special MRI technique has been developed to accurately reveal the three-dimensional microstructure of skeletal muscle, namely the diffusion tensor MRI (DTI) technique. The basic theoretical basis of DTI has been illustrated previously (13, 14). This technique sensitizes the MRI signal to water diffusion through motion-sensitizing gradients along different directions. Cells in muscles have elongated structures while presenting regularly oriented barriers to water diffusion, and the effect of cell membranes on diffusion has a directional dependence, which gives rise to anisotropy in diffusion (15, 16). The anisotropic diffusion properties are indicated by a tensor quantity instead of a scalar quantity.

DTI can help to characterize physiological properties, tissue microstructure and architectural organization of skeletal muscle. It has been demonstrated that DTI can differentiate between functionally different muscles in the same region of the body on the basis of their diffusive properties (17). DTI has been applied to study muscle architecture and tissue microstructure of normal and injured muscle (8, 16, 18-29). However, there is still difficulties to be noted when clinically using this technique in skeletal muscle. The purpose of this article is to review the potential applications of DTI in skeletal muscle, including the three-dimensional morphological reconstruction, functional study under active or passive motion, the pathological investigation of skeletal muscle, as well as some technique challenges of DTI encountered.

Reconstruction 3D structure using DTI-based fiber tracking

DTI-based fiber tracking is extensively used to reconstruct skeletal muscle fibers, which is possibly due to the anisotropic diffusion of water within muscle tissue. As is known to all, water diffusion can be detected using a tensor model by measuring water diffusion in six or more noncollinear directions. Because water diffuses most readily along the longitudinal axis of the muscle fibers, the principle for DT-MRI muscle fiber tracking is based on the preferential diffusion of water (30). Thus, these data are used to reconstruct and render the path and orientation of muscle fibers rough computer modeling (31).

In vivo fiber tracking of muscle fibers is feasible and could potentially be applied to provide 3D architecture and study human muscle structure function relationships (20-22). As afore mentioned, Budzik et al. (22) reconstructed 3D architecture of a whole muscle using fiber tracking technique, and directly measured the diffusion values over the whole

thigh. Heemskerk et al. (19) used DTI fiber tracking of mouse muscle to measure the physiologic cross-sectional area (PCSA), pennation angle, and fiber length directly. Damon et al. (18) demonstrated that the pennation angle measurements made using DTI fiber tracking agreed with those obtained using direct anatomical inspection.

To date, muscle fiber tracking has still a number of technical challenges. It is critical to recognize these limitations, such as the underlying anatomy, image acquisition parameters, noise, image acquisition characteristics, artifact characteristics of the data, the diffusion gradient strength and duration, and the fat admixture as well as the fiber-tracking algorithm (21, 30, 32). Previously, Heemskerk et al. (33) proposed a method to determine the accuracy of individual muscle fiber tracing based on the location at which the fibers terminate, the fiber path, the fiber length, and similarity to the neighboring fibers, and revealed that the majority of fibers were tracked completely covering 89.4 ± 9.6% and 75.0 ± 15.2% of the aponeurosis area in the superficial and deep compartments respectively. They concluded that applications of the muscle fiber tracking technique include the exclusion of erroneous fiber-tracking results, quantitative assessment of data set quality, and the assessment of fiber tracking stop criteria. In future, the assessment algorithm will enable further studies toward accurately quantifying muscle architectural parameters, assessing the quality of new fiber-tracking algorithms, or using DTI-based muscle fiber-tracking data in mechanical models of muscle.

Detection of Diffusion values

Compared with conventional MRI, there are several important values to quantitatively detect in the DTI of skeletal muscle based on the DTI images, such as three eigenvalues (λ1, λ2, λ3), fractional anisotropy (FA), and apparent diffusion coefficient (ADC), ellipsoid eccentricity et al. The three eigenvalues describe the magnitude of the diffusion coefficient in three orthogonal directions. Generally, the λ1 value represents the diffusive transport along the long axis of the muscle fibers, and the λ2 and the λ3 value correspond to orthogonal water diffusion to the three-dimensional direction of λ1 in the muscle fibers (23, 34). λ3 has also been reported to depend on the physiological-cross sectional area or the average of the muscle fiber radius (35). FA value is calculated from the three eigenvalues: (14) $ADC=(\lambda1+\lambda2+\lambda3)/3$; $FA=\frac{\sqrt{3[(\lambda1-ADC)^2+(\lambda2-ADC)^2+(\lambda3-ADC)^2]}}{\sqrt{2(\lambda1^2+\lambda2^2+\lambda3^2)}}$

ADC values reflect regional cerebral structure and its development, but the commonest clinical application of diffusion imaging is for the acute evaluation of brain injury (13).

Cross-sectional area measurements of FA and ADC values obtained by positioning a region of interest (ROI) allow the assessment of only a small part of the muscle at a fixed level. Fiber tacking may represent an interesting tool to extract the muscular fibers from a single ROI and thus easily obtain the values of FA and mean ADC of these fibers (22). Previously, the mean FA values and ADC values of the thigh muscles (Tab.1) and leg muscles (Tab.2) have been in-depth studied. Sinha et al. (20) measured FA and ADC values by positioning a region of interest (ROI). Differently, Budzik et al. (22) provided *in vivo* 3D architecture of human thigh muscles using tractography on a 1.5T magnet, and obtained the value of tractography images to obtain FA and ADC values over the whole thigh.

Thigh Muscles	ADC (*10^{-3} mm^2/s)	FA
Sartorius	0.9l ± 0.26	0.35 ± 0.09
Gracilis	0.76 ± 0.23	0.35 ± 0.11
Rectus femoris	0.92 ± 0.20	0.29 ± 0.08
Vastus intermedius	0.96 ± 0.24	0.28 ± 0.08
Vastus medialis	0.87 ± 0.21	0.27 ± 0.08
Vastus lateralis	0.92 ± 0.21	0.27 ± 0.09
Adductus	0.96 ± 0.26	0.28 ± 0.09
Biceps femoris short head	0.90 ± 0.29	0.38 ± 0.11
Biceps femoris long head	0.89 ± 0.31	0.29 ± 0.10
Semitendinous	0.88 ± 0.31	0.30 ± 0.09
Semimembranous	0.85 ± 0.30	0.34 ± 0.10

ADC, mean apparent diffusion coefficient; FA, fractional anisotropy.

Table 1. Mean FA and ADC values of the thigh muscles (cited from Budzik et al.) (22)

Leg Muscles	ADC (*10^{-3} mm^2/s)	FA
Tibialis anterior	1.56 ± 0.09	0.28 ± 0.01
Gastrocnemius medial	1.59 ± 0.04	0.30 ± 0.03
Gastrocnemius lateral	1.67 ± 0.10	0.33 ± 0.03
Soleus medial	1.53 ± 0.08	0.25 ± 0.04
Soleus lateral	1.65 ± 0.20	0.18 ± 0.04

ADC, mean apparent diffusion coefficient; FA, fractional anisotropy.

Table 2. Mean FA and ADC values of the leg muscles [cited from Sinha et al. (20), λav equates the mean apparent diffusion coefficient (ADC)].

Functional study of muscle biomechanics

Compared with the traditional MRI imaging, one of the advantages is the capability of DTI in investigating the muscle biomechanics. This technique enables the reconstruction of a muscle structure, which is able to determine the force and velocity potentials of the muscle. Three-dimensional analyses of strain with respect to the fiber structure are important to characterize skeletal muscle contraction *in vivo*. Contraction of muscles produces changes in DTI parameters, which are related to the physiological state of the muscle (36). It has been demonstrated that changes in muscle microstructure associated with passive extension and contraction would affect proton diffusivity, and this alteration of diffusiv-

ity could be detected by measuring ADC (37). This alteration of diffusivity is probably associated with microscopic structural changes of the muscle (35).

Recent studies have also identified that the three eigenvalues and FA value would change with passive or active shortening and stretching of the muscle. Regarding the eigenvalues of DTI, λ2 and λ3 showed significant changes in relation to muscle length whereas no change in λ1 could be found (38). Deux et al. investigated the effect of an active plantarflexion on the medial gastrocnemius, and observed three eigenvalues (λ1, λ2, λ3) increased while FA value decreased (36). In another research studying the passive motion effect on medial gastrocnemius, (37) λ1 and λ3 decreased with passive plantar-flexion while λ2 did not change, and FA value became lower as well. More recently, Okamoto et al. (34) investigated the effect of active contraction using DTI and concluded that the higher FA, λ1 and λ2 values of muscles at contraction than rest presumably reflect complicated changes, including microscopic morphological changes of the diffusion-restricting factor, focal temperature, and perfusion. Kan et al. (31) investigated the feasibility of using DTI based muscle fiber tracking and physiological cross sectional area (PCSA) to predict biomechanical resultant force vectors, as well as substantiate muscle architectural differences, of components of the quadriceps mechanism in healthy volunteers and in patients with symptomatic recurrent lateral patellar dislocation (LPD). They showed that biomechanical models of the quadriceps mechanism in patients with chronic LPD and healthy subjects can be created in healthy subjects and patients with chronic LPD using DTI and DTI muscle fiber tracking can detect biomechanical vector force differences between healthy subjects and subjects with LPD.

Pathological investigation of skeletal muscle

DTI is a favorable technique to assess human muscle injury, which resulted in decrease of FA value and increase of ADC value (25). McMillan et al. (39) assessed damage in healthy and dystrophic skeletal muscle after lengthening contractions using DTI, and they suggested that DTI is an accurate indicator of muscle injury, even at early time points where the MRI signal changes are dominated by local edema. Heemskerk et al. (23) investigated whether and how the indices that can be measured by DTI respond to ischemia of skeletal muscle followed by reperfusion. They found that The DTI indices dynamically changed in response to ischemia-reperfusion of mouse skeletal muscle, and ADC decreased during ischemia and increased upon reperfusion. These results demonstrated that DTI can be used to assess ischemia-induced damage to skeletal muscle. Subsequently, Heemskerk et al. (24) prospectively evaluated skeletal muscle injury and repair in mice after femoral artery ligation using quantitative DTI. They observed that the diffusion-tensor indexes changed dynamically in association with the severity and location of muscle damage after femoral artery ligation, and suggested that DTI could be applied as an *in vivo* marker and as a diagnostic tool for assessment of ischemia-induced muscle damage.

Previously, Zeng et al. (27) applied DTI to distinguish the edema, injury and rupture in the traumatic skeletal muscle fiber using rabbit model, and found that there were significant differences between groups regarding the ADC and FA values (Tab.3). After tractography, they observed that the tracking cross-fiber could be seen but it decreased slightly in the edema muscle, the tracking fiber decreased markedly in the injury muscle, and the transverse-orientation tracking fiber vanished yet some interrupted longitudinal-orientation tracking fiber could be found in the ruptured muscle. These changes in diffusion tensor characteristics (such as ADC and FA) are consistent with cellular damage and inflammation resulting in a less ordered and less restricted tissue (26). However, not all muscle insults result in increased ADC and decreased FA. In a study investigating the diffusion anisotropy and microscopic structure of atrophied skeletal muscles by denervation, Saotome et al. (28) found the denervated group had significantly higher FA compared with the control group and no significant difference in the mean diffusivity and the ADC between groups. These results suggest that the self-diffusion coefficient (ADC) of water in muscle fibers is not affected by muscle atrophy and muscle atrophy resulted in a geometrical change in the cell membranes.

Muscle	ADC ($*10^{-3}$ mm^2/s)	FA
Normal	6.12 ± 1.34	0.42 ± 0.12
Edema	6.38 ± 1.30	0.36 ± 0.12
Injury	8.06 ± 0.97	0.26 ± 0.09
Ruptured	9.57 ± 0.93	0.12 ± 0.08

ADC, mean apparent diffusion coefficient; FA, fractional anisotropy.

Table 3. Mean FA and ADC values of rabbit skeletal muscle with or without injury (cited from Zeng et al.) (27).

Technique challenges - Scan parameters

One of the difficulties of the DTI application is to find the most optimal scan parameters [mainly the echo planar imaging (EPI) sequence], in order to get a clear and accurate imaging. Here we have summarized several scan parameters with different MRI machines (Tab.4). Moreover, the effect of DTI greatly depends on the MRI machine. It might be suggested to design an individual scan parameter in different machines.

Different from the DTI in the brain, there are several technique challenges presented in the detection of skeletal muscle (20). At first, the signal-to-noise ratio (SNR) is a limiting factor in muscle imaging because muscle has low T2 compared to brain tissue. Further improvements in SNR were realized by increasing the number of averages to 16 and imaging at high fields (3.0T) (20). The major improvements in the acquisition were the use of 10 gradient directions to improve the eigenvector determination and the use of surface coils to obtain higher SNR (33). Rationale for DTI Sequence Parameters (40): for the muscle has short T2 value,

	Machine	TR(ms)/ TE(ms)	FOV (cm)	Matrix	NEX	Slice Thickness (mm)	Gradient directions	*b*-value (s/mm^2)
Galban[8] 2005	1.5T Siemens Sonata	2000 / 95	180*135	128*96	16	6	6	400
Sinha[20] 2006	3.0T Siemens Magnetom Trio	3300 / 69	200*165	128*128	16	5	6	600
Lansdown[21] 2007	3.0T Philips Intera Achieva	5000 / 42	180*180	64*64	2	7.5	6	500
Budzik[22] 2007	1.5T Philips Achieva	6277 / 60	200	128*128	---	8	32	400
Hatakenaka[35] 2008	1.5T Philips Intera Achieva	4000 / 56	200	128*128	6	10	6	500
Heemskerk[33] 2009	3.0T Philips	3300 / 48	192*192	96*64	---	6	10	500
Okomoto[34] 2010	1.5T Philips Achieva	2500 / 59	400	128*128	---	6	6	500
Heemskerk[32]	3.0T	3300 / 48	192 * 192	96 *64	4	6	10	500

Table 4. Scans were acquired using an echo-planar imaging (EPI) sequence.

(Continued)

(Continued Table 4)

	Philips							
2010								
Sinha[40]	1.5 T	5000 / 46	240	128 * 128	---	5	6	500
2011	GE							
Sinha[16]	3.0T	6400 / 48	240	128 * 128	6	5	13	500
2011	GE							

TR, repetition time; TE, echo time; FOV, field of view (FOV); NEX, number of excitation.

a low TE can ensure sufficient SNR for DTI measurements. When muscle DTI data are acquired at SNR<60, there are b-value-dependent errors in estimating the tensor and its derived indices and the estimated principal eigenvector differs from the true direction (41). The optimum "b" values in terms of minimizing variance in DTI are 435~725 s/mm^2 (30). A lower b-value (compared to the routinely used 1000 s/mm^2 in brain DTI) is chosen for muscle imaging for one focus of the sequence design is to minimize TE to maximize SNR of the low T2 muscle. Future in-depth investigations are required to concentrate in the set of these technique parameters in order to get the optimal DTI imaging.

Conclusions and perspectives

In summary, DTI technique has a great potential to characterize physiological properties, tissue microstructure and architectural organization of skeletal muscle. Here, we reviewed several DTI studies in skeletal muscle and summarized the main applications in clinics. Using DTI technique, several diffusion values of skeletal muscle can be directly obtained, and these values have a great association with the muscle physiology and pathology. Furthermore, it is possible to non-invasively study the three-dimensional architecture of skeletal muscle by making fiber tracking. In particular, DTI is able to analyze muscle biomechanics *in vivo* compared with the traditional MRI imaging. To date, DTI has been utilized to analyze the differences in diffusion properties between non-injured and injured muscles, fatigued muscles, or muscle of young and old subjects, ischemia of skeletal muscle. Collectively, it is reasonable to believe that DTI has a great potential to study physiological properties and tissue microstructure, and our investigations may arouse in-depth studies on the clinical application of DTI in skeletal muscle in future.

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