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Research article

Improvement of Reliability of Diffusion Tensor Metrics in Thigh Skeletal Muscles

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ABSTRACT

Objective: Quantitative diffusion tensor imaging (DTI) of skeletal muscles is challenging due to the bias in DTI metrics, such as fractional anisotropy (FA) and mean diffusivity (MD), related to insufficient signal-to-noise ratio (SNR). This study compares the bias of DTI metrics in skeletal muscles via pixel-based and region-of-interest (ROI)-based analysis.

Methods: DTI of the thigh muscles was conducted on a 3.0-T system in N = 11 volunteers using a fat-suppressed single-shot spin-echo echo planar imaging (SS SE-EPI) sequence with eight repetitions (number of signal averages (NSA) = 4 or 8 for each repeat). The SNR was calculated for different NSAs and estimated for the composite images combining all data (effective NSA = 48) as standard reference. The bias of MD and FA derived by pixel-based and ROI-based quantification were compared at different NSAs. An "intra-ROI diffusion direction dispersion angle (IRDDDA)" was calculated to assess the uniformity of diffusion within the ROI.

Results: Using our standard reference image with NSA = 48, the ROI-based and pixel-based measurements agreed for FA and MD. Larger disagreements were observed for the pixel-based quantification at NSA = 4. MD was less sensitive than FA to the noise level. The IRDDDA decreased with higher NSA. At NSA = 4, ROI-based FA showed a lower average bias (0.9% vs. 37.4%) and narrower 95% limits of agreement compared to the pixel-based method.

Conclusion: The ROI-based estimation of FA is less prone to bias than the pixel-based estimations when SNR is low. The IRDDDA can be applied as a quantitative quality measure to assess reliability of ROI-based DTI metrics.

1. Introduction

Diffusion tensor imaging (DTI) [1] is considered a valuable diagnostic tool for examining integrity of organized tissues, such as cerebral white matter, peripheral nerves and skeletal muscles. Quantitative DTI metrics, such as fractional anisotropy (FA) and mean diffusivity (MD) are used in both research and clinical settings [2–6]. Skeletal muscles can be affected by a variety of disorders, such as myositis, denervation change, rhabdomyolysis, trauma, and compartment syndrome, etc. [7] and the associated qualitative signal changes on conventional T1-weighted and T2-weighted images can be non-specific. In recent years, there has been increased interest in DTI of skeletal muscles, as it can

Abbreviations: BF, biceps femoris muscle; DTI, diffusion tensor imaging; FA, fractional anisotropy; G, gracilis muscle; GRE, gradient echo sequence; HIPAA, health insurance portability and accountability act; IRDDDA, intra-ROI diffusion direction dispersion angle; IRB, institutional review board; LOA, limits of agreement; MD, mean diffusivity; MRI, magnetic resonance imaging; NSA, number of signal averages; RF, rectus femoris muscle; ROI, region-of-interest; SM, semimembranosus muscle; SNR, signal-to-noise ratio; ST, semitendinosus muscle

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Table 1
Six-point Likert scale for assessment of DTI quality.

0	Excessive motion artifacts and fat contamination, FA and MD quantification not possible
1	No apparent motion artifacts, residual fat signal on diffusion weighted images contaminated more than 50% muscles areas
2	No apparent motion artifacts, residual fat signal on diffusion weighted images contaminated 25–50% muscles areas
3	No apparent motion artifacts, residual fat signal on diffusion weighted images contaminated 15–25% muscles areas
4	No apparent motion artifacts, residual fat signal on diffusion weighted images contaminated 5–15% of muscles areas
5	No apparent motion artifacts, residual fat signal on diffusion weighted images contaminated less than 5% muscles areas

deliver quantitative information as well as provide insight into the internal architecture of muscles using tractography [8–13]. Changes in muscle DTI have already been reported with aging [5,14], injury [15,16], disease [17,18], and extensive exercise [6,19,20].

In DTI quantitation, sufficient signal-to-noise ratio (SNR) is essential for accurate measurements [18]. In addition, the tissue properties of skeletal muscle differ from heavily studied cerebral tissue, with higher diffusivity of water and lower FA, which can result in higher likelihood of bias in DTI metrics [21]. In standard DTI processing, FA and MD are calculated for each pixel, then averaged over a region-of-interest (ROI), the so-called "pixel-based" approach. Alternatively, in an ROI-based method, the signal of the b = 0 image and all diffusion weighted images of each direction can be averaged over the ROI before diffusion tensor calculation to obtain the corresponding FA and MD [22]. The latter approach reduces the noise due to the spatial signal averaging and potentially mitigates the uncertainty of the result. This method assumes that the ROI is inside a single muscle, the muscle fibers within the ROI are nearly parallel to each other, and the diffusion properties are uniform.

We hypothesize that the number of signal averages (NSA), which affects SNR, influences the reliability of DTI metrics obtained from the two quantification methods.

The aim of this work was to compare the bias of DTI metrics at different NSA in skeletal muscles obtained with pixel-based and ROI-based analyses.

2. Materials and methods

2.1. Subjects

This is a HIPAA compliant IRB approved prospective study. Informed consent was obtained from each subject. Eleven healthy volunteers (male: female = 6:5, age 31.5 ± 4.0 years) were studied. None of the subjects had restless leg syndrome, known myopathy, denervation change, local infection, tumor or neuropathy. None of the subjects had performed excessive exercise in the five days prior to the MRI-scan. Subjects were imaged from January 2016 to November 2016.

2.2. Diffusion tensor imaging of the thigh skeletal muscle

Magnetic resonance imaging (MRI) scans were acquired on a 3.0-T scanner (Ingenia, Philips, Best, Netherlands; software release 5.7.1.2). Subjects were examined in supine position and feet first using a 28-channel sensitivity encoding torso array coil placed anteriorly. The field of view (FOV) was at mid-thigh level; anatomic gradient echo sequence (GRE) and DTI sequences were acquired using the same geometry. The protocol included:

(i) Reconstructed axial 3D GRE modified Dixon sequence (TR/TE/ΔTE 4.4/1.18/2.6 ms, flip angle 3°, FOV 250 × 250 mm^2 with voxel 2.0 × 1.0 × 0.5 mm, NSA = 1 and acquisition time 2:12 min: sec). Post-processing produced in- and opposed-phase based water- and fat-only images.
(ii) Axial fat-suppressed single-shot spin-echo echo planar imaging (SS SE-EPI) sequence (TR 2433–4565 ms, (minimum TR was used which depends on number of slices), TE 66 ms, FOV 224 × 224 mm^2, acquisition matrix size 112 × 112 mm, water-fat-shift = 32 mm, b = 0 and 500 s/mm^2, 15 diffusion encoding directions, 20–33 slices with a thickness of 6 mm and a slice gap of 0 mm, SENSE factor = 2. Acquisition time for NSA = 4 and NSA = 8 varied from 6–7 min to 12–15 min, respectively.

For each subject, eight DTI scans were acquired with NSA = 8, 8, 8, 8, 4, 4, 4, 4. Our typical DTI protocol requires one DTI data set with NSA = 4 or 8, needing approximately 7 min or 15 min of acquisition time. In this investigation, we repeated scans to assess reproducibility, and to construct a data set with low noise level as a standard reference. The total scan duration for each patient was approximately 90 min.

2.3. Data analysis

All DTI scans were registered relative to each other to remove effects of motion during acquisition for each subject using the PRIDE tool [23]. Data processing was performed using internally developed software written in IDL 8.3 (Exelis IVS, Boulder, CO). In addition to analyzing the originally acquired data sets of each subject, a data set with an effective NSA of 48 was constructed by a weighted summation of the original 8 image sets, and used to represent the reference standard.

Motion artifacts and fat suppression inhomogeneities were classified visually by two readers blinded to DTI results using a six-point Likert scale as illustrated in Table 1. For quantification of DTI metrics, ROIs were drawn manually on the rectus femoris (RF), semitendinosus (ST), semimembranosus (SM), biceps femoris (BF), and gracilis (G) muscle by two independent readers (Fig. 1). ROIs obtained by freehand following the shape of the muscle, typically encompassed more than 50% of the cross-sectional muscle area and were applied exactly to all data sets relatively aligned to each other. In general, fat suppression in DTI is similarly effective as in other pulse sequences. However, fat signal can be more obvious on diffusion weighted images (b = 500 s/mm^2) than on b = 0 s/mm^2 images, mainly because fat molecules are much larger than water molecules and have a very low diffusion coefficient. On the other hand, due to a chemical shift effect, subcutaneous fat can protrude into muscle and render the affected areas unusable for quantification. Areas of fat contamination due to incomplete suppression of subcutaneous fat and the water-fat shift on EPI readout were carefully

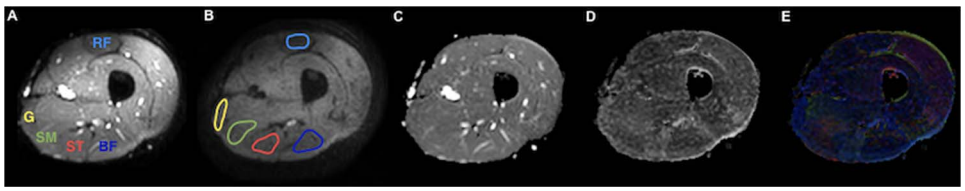

Fig. 1. Axial thigh cross-section images of a 34-year-old male volunteer with exemplary annotation of muscle ID and corresponding regions-of-interest (ROIs). DTI image (b = 0 s/mm^2) (A), diffusion-weighted image (b = 500 s/mm^2) (B), mean diffusivity map (C), gray-scale FA-map (D) and color-coded FA map (E). Residual fat suppression and motion rated with a six-point Likert scale on (B).
Abbreviations: BF, biceps femoris muscle; G, gracilis muscle; RF, rectus femoris muscle; SM, semimembranosus muscle; ST, semitendinosus muscle.

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