Time-dependent diffusion as a biomarker for rotator cuff atrophy

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Purpose: **To move from subjective empirical to objective microstructural markers of rotator cuff muscle atrophy.** While diffusion tensor imaging (DTI) is used to assess soft tissue pathology, it has not realized its full potential in assessing myofiber structural damage. Recently, the framework to determine myofiber diameter and membrane permeability from time-dependent DTI(t) using the random permeable barrier model[4] (RPBM) was proposed[1,2] and applied in compartment syndrome[3]. Here we utilize this framework to: **(1)** determine if it is feasible to quantify myofiber diameter of supraspinatus (SUP) and infraspinatus (INF) muscles in the rotator cuff in normal volunteers in a clinically acceptable time period; **(2)** determine if RPBM+DTI(t) can be used to objectively demonstrate changes that occur in the musculature following rotator cuff repair.
Target Audience: MSK radiologists and orthopaedic surgeons who treat patients with rotator cuff pathology; diffusion microstructure researchers.

Methods: **(1)** 6 asymptomatic volunteers consisting of 3 males/3 females with a mean age 30.7 (range 23-44) for a total of 10 shoulders [5 right; 5 left] were scanned on a MAGNETOM Trio 3T Tim system (Siemens AG, Erlangen, Germany). They were scanned using a dedicated 4 channel shoulder coil with the following protocol: coronal FS T2W, sagittal T1W and sagittal DTI from STEAM EPI diffusion preparation along 5 diffusion times *t* ranging from 57-1000 ms. Diffusion weighted images were acquired for *b*=0, and along 12 gradient directions for *b*=500 s/mm^2. Other DTI acquisition parameters include TR > 5000 ms, TE= 40.4 ms, matrix size=64x64, FOV= 190x190 mm^2, 10 slices, and voxel size 3x3x5 mm^3. Total acquisition time of DTI(t) was 9 minutes. Regions of interest [ROIs] were drawn on T1W sagittal images along the borders of the SUP and INF [Fig. 1A,B] and then overlaid onto DWI for extracting average ROI-values.
(2) 2 patients [60 yr male, 60 yr female] with full thickness tears of the rotator cuff were imaged within two weeks prior to rotator cuff repair, and then again 3 months after the repair with a similar protocol. Here we acquired 7 diffusion times *t* in the range 57-1000 ms. Rotator cuff pathology and image quality was reviewed by a board certified radiologist. Total acquisition time was **13 minutes**.
The average value of the diffusivity transverse to the sarcolemma as a function of *t*, $D_\perp(t)$, was used for each ROI to fit to RPBM [Fig. 1C], from which an average myofiber diameter (μm) per ROI was inferred. Previous histologic studies have shown no statistically significant difference in the size of the SUP and INF myofibers[4].

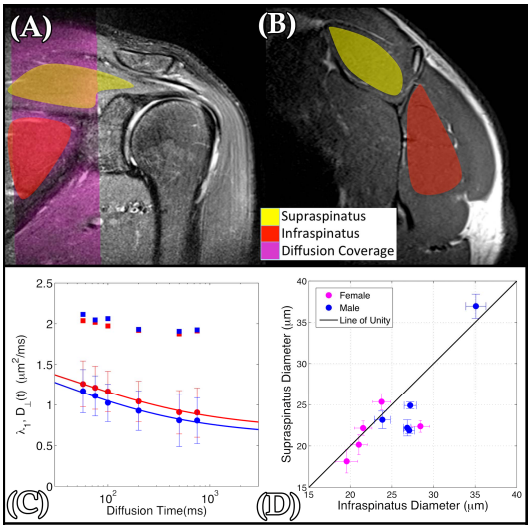
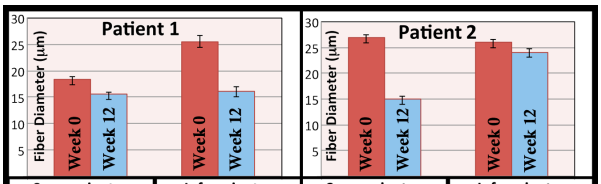


Figure 1: **(A)** Coronal FS T2W image showing ROIs (supraspinatus-yellow; Infraspinatus- red) and diffusion coverage (purple). **(B)** Sagittal T1w image in the region of diffusion coverage showing ROIs **(C)** Example of time-dependent parallel and transverse diffusion $D_\perp(t)$ in the infraspinatus for patient 2 at week 0 (red) and week 12 (blue). **(D)** Comparison between infraspinatus and supraspinatus fiber diameters.

Results: (1) The mean myofiber diameter of the SUP was 23.0 μm and 24.4 μm for INF. The mean ± standard deviation (range) of difference between the two muscles was -0.86 ± 2.45 (-3.75 to 2.20) μm [Fig. 1D]. The 95% confidence interval for mean diameter difference was -3.52 to 1.81 μm. **(2) There was a decrease in myofiber size of SUP and INF myofiber diameters between the preoperative and postoperative scans** [Fig. 2]. For patient 1 (injury on left), SUP atrophied by 15.17%, while INF atrophied by 36.9%. For patient 2 (injury on right), SUP atrophied by 44.4%, while INF atrophied by 7.3%.

Discussion: DTI(t)+RPBM framework is shown to robustly quantify the myofiber diameter of the supraspinatus and infraspinatus musculature in normal volunteers; no significant difference was demonstrated between these muscles [Fig.1 D], consistent with literature[4]. Given the 13 min scan time, DTI(t) can be added to standard MR shoulder protocols without significant change in workflow. Inclusion of coils with more channels, multiband, and further optimization of the sequence could further speed the protocol. DTI(t) + RPBM was able to capture the anticipated atrophy in rotator cuff musculature in the early postoperative period after rotator cuff repair for both of the clinical patients. **Additionally, DTI(t) provides a more objective biomarker for assessing the status of the rotator cuff musculature in the setting of tendon tearing and repair compared to the current gold standard, subjective grading on MR imaging [6,7].**



Supraspinatus	Infraspinatus	Supraspinatus	Infraspinatus
18.3626 ± 0.5992	25.4372 ± 0.3205	26.8991 ± 0.5909	25.9523 ± 0.5268
15.5763 ± 1.2198	16.0484 ± 0.8986	14.9659 0.6937	24.0613 ± 0.7300

Figure 2: Histogram of myofiber diameters showing microstructural atrophy after 12 weeks.

Conclusion: Time-dependent diffusion MRIDTI combined with RPBM modeling paradigm provides an objective microstructural evaluation of the rotator cuff musculature, and, in turn, the degenerative changes that can occur in the setting of tendon tearing and after surgery. This may play a role in patient selection for surgery and help assess the healing potential for current repair methods without adding significant scanning time to standard MR shoulder protocols.

References: [1] Fieremans et al, ISMRM (2013) 0489; [2] Lemberskiy et al, ISMRM (2014) 4423 (2014); [3] Novikov et al. Nat Phys 7: 508, 2011; [4] Sigmund, E. *et al.* JMRI 27(5): 519-528, NMR in biomedicine (2014); [5] Johnson et al. J Neurol Sci 18:111–129, 1973; [6] Goutallier et al. Clin Orthop Relat Rad 304: 78–83, 1994; [7] Spencer et al. Am J Sports Med 36: 99-103, 2008.