Effect of Supraspinatus Tendon Injury on Supraspinatus and Infraspinatus Muscle Passive Tension and Associated Biochemistry

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Background: Injury to the supraspinatus and infraspinatus tendons and the associated atrophic changes to the muscle remain a common clinical problem. Specifically, increased muscle stiffness has been implicated in failure of the repair and poor functional outcomes. We present a comparison of the passive mechanical properties and associated biochemical studies from patients with and without torn supraspinatus tendons.

Methods: Muscle biopsy samples (n = 40) were obtained from twenty patients undergoing arthroscopic shoulder surgery. Passive mechanical tests of both individual fibers and fiber bundles as well as analysis of titin molecular weight and collagen content were performed.

Results: At the fiber-bundle level, a significant increase in passive modulus was observed between intact supraspinatus samples (mean [and standard error], 237.41 ± 59.78 kPa) and torn supraspinatus samples (515.74 ± 65.48 kPa) ($p < 0.05$), a finding that was not observed at the single fiber level. Within the torn samples, elastic moduli in the supraspinatus were greater than in the infraspinatus at both the single fiber and the fiber-bundle level. There was a significant positive correlation between bundle elastic modulus and collagen content ($r^2 = 0.465$) in the supraspinatus muscle as well as a significant positive correlation between tear size and bundle elastic modulus ($r^2 = 0.702$) in the torn supraspinatus samples.

Conclusions: Supraspinatus muscle passive tension increases in a tendon tear size-dependent manner after tendon injury. The increase in muscle stiffness appears to originate outside the muscle cell, in the extracellular matrix.

Clinical Relevance: Muscle stiffness after rotator cuff tendon injury is more severe with large tears. This finding supports the concept of early intervention, when tendon tears are smaller, and interventions targeting the extracellular matrix.

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Rotator cuff musculature plays a vital role in stabilizing the shoulder joint and is a common site of injury, especially among the elderly[1]. Degenerative changes occur with increasing age[2], but acute injury remains a problem for all age groups. Rotator cuff tears lead to weakness[3], decreased range of motion[4], pain, and functional deficiencies[5]. Harryman et al.[4] and Gerber et al.[6] reported that the integrity of the repair, not the size of the initial tear, is closely linked to the functional outcome of the rotator cuff repair. However, success rates for repairs are limited, in part, because of the changes in stiffness

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and retraction of the muscle and tendon after the tendon injury[7]. The difficulty in repairing traumatic massive rotator cuff tears has been documented as early as six weeks after the initial injury[8]. Data from human and animal models have suggested that whole muscle stiffness increases when the tendon is torn and as the severity of the tear increases[6,9-14]. Although increases in stiffness have been associated with whole muscle connective tissue content[11], it remains unclear whether these changes are caused by fibrosis, shortened muscle fibers, or changes in the material properties of the fibers themselves[15,16]. Data from previous studies involving rabbit muscle have demonstrated a correlation between the molecular weight of titin and single fiber stiffness[17], and some data have indicated that whole muscle collagen content is elevated in muscles with greater passive tension[11]. However, these adaptations have been poorly studied in rotator cuff disease in humans. The authors of a previous study compared the material properties of single fibers and fiber bundles from massive supraspinatus tears with single fibers and fiber bundles from the deltoid muscle[18]. Although the authors found no significant differences between the deltoid and supraspinatus muscles, this comparison with the deltoid is problematic because different human muscles have different passive mechanical properties[19], and their analytical method involved sarcomere lengths that were supraphysiologic. Therefore, the purpose of this current study was to compare the passive mechanical properties of the supraspinatus and infraspinatus muscles with intact and torn supraspinatus tendons.

Materials and Methods

Subjects

Under a protocol approved by the University of California, San Diego, Human Subjects Protection Program, muscle samples were obtained from twenty patients undergoing arthroscopic shoulder surgery (Table I). Inclusion criteria were patient willingness to participate in the study and arthroscopic access to the shoulder allowing biopsy of the supraspinatus and infraspinatus muscles. Subjects in the tear group were identified by clinical examination, findings on magnetic resonance images, and surgical confirmation of a rotator cuff tear. For the sixteen subjects for whom the date of injury was known, the average duration of symptoms was 13.7 ± 3.4 months. The tear size was quantified by multiplying the largest anteroposterior dimension on a sagittal oblique image by the largest mediolateral dimension on a coronal oblique image of the supraspinatus and infraspinatus tendons. The subjects who were placed in the intact (control) group had no identifiable rotator cuff tear on either images or during surgery and were undergoing arthroscopic surgery for another indication. Exclusion criteria were calcific tendinitis of the supraspinatus and infraspinatus (one patient) as well as subacromial inflammatory bursitis (one patient). These two patients were excluded because their intraoperative findings were consistent with an acute inflammatory process that was not observed in any other patients.

Specimen Collection and Preparation

Supraspinatus and infraspinatus muscle groups were identified, and small (approximately 50-mg) biopsy samples were obtained from each muscle with use of an arthroscopic rongeur 1 to 2 cm proximal to the musculotendinous junction (see Appendix). After harvest, the biopsy sample was immediately placed in a relaxing solution composed of ethylene-glycol tetra-acetic acid (7.5 mmol/L), potassium propionate (170 mmol/L), magnesium acetate (2 mmol/L), imidazole (5 mmol/L), creatine phosphate (10 mmol/L), adenosine triphosphate (4 mmol/L), leupeptin (a protease inhibitor, 17 mg/mL), and E64 (a protease inhibitor, 4 mg/mL)[20]. This solution prevented depolarization across any site of disrupted membrane as well as proteolytic degradation, either of which can destroy a specimen. Single fibers or fiber bundles were immediately dissected from the fresh biopsy sample or were placed into a storage solution composed of relaxing solution mixed with 50% glycerol and stored at −20°C. Samples stored in this manner have stable mechanical properties for up to three months[20,21]; nonetheless, all of the fibers in this study were tested within fourteen days.

TABLE I Patient Demographics

Characteristic	Supraspinatus	
	Intact	Torn
Age* *(yr)*	46 ± 9	53 ± 8
Sex		
Male	5	10
Female	2	3
Height* *(cm)*	166.9 ± 10.5	170.9 ± 10.1
Weight* *(kg)*	80.9 ± 18.9	78.5 ± 14.6
BMI* *(m^2/kg)*	28.9 ± 5.4	26.7 ± 3.8
Supraspinatus tear	7	13
Infraspinatus (intact/torn)	7/0	11/2
Extent of tear		
Partial	—	8
Full thickness	—	5
Tear size* *(mm^2)*	0	206.6 ± 130.9
Duration of shoulder symptoms* *(mo)*	10.1 ± 7.6	15.3 ± 11.0

*Values are given as the mean and standard deviation for the twenty observations. BMI = body mass index.

Passive Single Fiber and Fiber-Bundle Mechanics

The single fiber and fiber-bundle testing protocol was designed to measure elastic material properties apart from any velocity-dependent properties, as previously described[19,22,23]. Briefly, the dissected single fiber or fiber-bundle segment was secured on either side to 125-μm titanium wires with use of 10-0 silk suture loops. One wire was secured to an ultrasensitive force transducer (sensitivity, 10 V/g; model 405A, Aurora Scientific, Aurora, Ontario, Canada), and the other was secured to a micromanipulator. The sample was transilluminated by a 7-mW helium-neon laser to permit sarcomere-length measurement by laser diffraction[24]. Resolution with this method is approximately 5 nm[25]. The system was calibrated with a 2.50-μm plastic blazed diffraction grating prior to experimentation (Diffraction Gratings, Nashville, Tennessee). After calibration and mounting, the samples were lengthened until force registered on a load cell that defined baseline load and slack sarcomere length. Baseline sample diameters were optically measured with a crosshair reticule mounted on a dissecting microscope and micromanipulators on an x-y mobile stage. Force-displacement data were generated for each mounted sample in 250-μm increments. Then stress-relaxation was permitted for two minutes, and both sarcomere length and tension were again recorded. The segments were elongated through the theoretical limit of actin and myosin overlap in human muscle[26]. Force data were converted to stress by dividing force by the baseline cross-sectional area value, and displacement was converted to strain by subtracting sarcomere length from the baseline value for slack sarcomere length

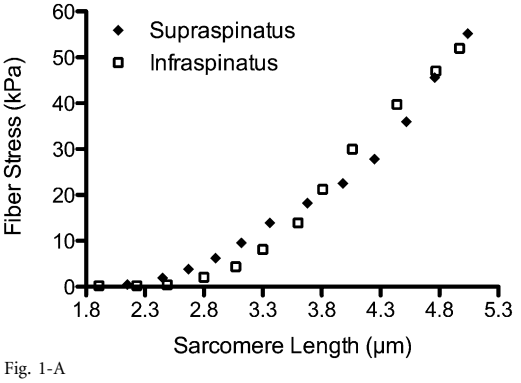

Fig. 1-A

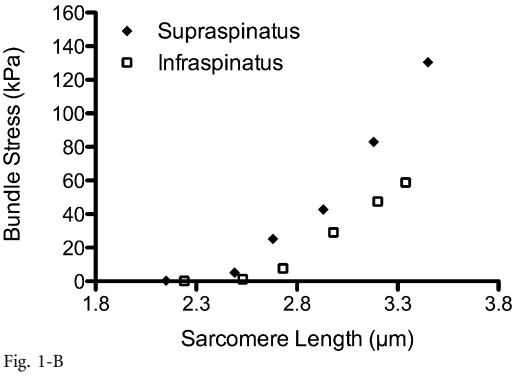

Fig. 1-B

An example of stress-sarcomere length plots for single fibers (Fig. 1-A) and fiber bundles (Fig. 1-B).

and then dividing by the baseline value for slack sarcomere length (Figs. 1-A and 1-B). Stress-strain curves were then fit with quadratic polynomials (average r^2 values, 0.985 to 0.995) before mechanical variables were extracted. Elastic modulus values were obtained at 3.2 μm, as that is the sarcomere length of the supraspinatus and infraspinatus in the neutral shoulder position[27]. Samples were discarded if they did not produce a clear diffraction pattern, if any irregularities appeared along their length, or if they were severed or slipped (visible in the force record) at either suture attachment point during the test.

Analysis of Titin Isoform

Single fibers were homogenized in sodium dodecyl sulfate-vertical agarose gel electrophoresis (SDS-VAGE) sample buffer and stored at −80°C until they were analyzed with gel electrophoresis. SDS-VAGE sample buffer comprised 8 M urea, 2 M thiourea, 3% SDS wt/vol, 75 mM dithiothreitol 0.03% bromophenol blue, and 0.05 M Tris-Cl (pH, 6.8)[28]. The molecular mass of titin in single fibers was determined with use of SDS-VAGE. This procedure has been described previously[28]. An acrylamide plug was placed at the bottom of the gel to hold the agarose in place. The final composition of this plug was 12.8% acrylamide, 10% vol/vol glycerol, 0.5 M Tris-Cl, 2.34% N,N′-diallyltartardiamide, 0.028% ammonium persulfate, and 0.152% tetramethylethylenediamine. The composition of the agarose gel was 1% wt/vol SeaKem Gold agarose (Lonza, Basel, Switzerland), 30% vol/vol glycerol, 50 mM Tris-base, 0.384 M glycine, and 0.1% wt/vol SDS. This solution was poured over the acrylamide plug and was kept warm to prevent premature solidification.

Titin standards were obtained from human cadaveric soleus and rat cardiac muscle, which have known molecular weights of 3700 and 2992 kDa, respectively, based on sequence analysis of the 300-kb titin gene with a coding sequence contained within 363 exons[29,30]. These tissues were also homogenized and stored at −80°C until analysis. Before they were loaded onto the gel, a titin standard "cocktail" was created by placing 4 μL of human soleus standard and 8 μL of rat cardiac standard into 98 μL of sample buffer. Sample wells were then loaded with both the biopsy sample and rat cardiac homogenate. Human soleus and rat cardiac titin homogenates were loaded into standard lanes. This facilitated titin quantification on each gel. Gels were run at 4°C for five hours at a constant current of 15 mA.

Agarose gels were fixed and stained according to the Silver Stain Plus (Bio-Rad, Hercules, California) procedure[31], except that the gels were dried for approximately twenty hours at 40°C immediately after fixing. The gels were subsequently rinsed and stained as described in the Silver Stain Plus procedure. Relative mobility and intensity of each band were quantified with use of a GS-800 Calibrated Densitometer and Quantity One 1-D Analysis software (both, Bio-Rad).

Relative mobility of protein on the gel was linearly related to the log of their molecular mass. The gel regression relationship was calculated based on the three standard lanes containing human soleus titin and rat cardiac titin. Relative mobilities of the biopsy samples were calculated based on their relative position compared with standards. The molecular mass of the unknown band was calculated from the relative mobility and the regression equation.

Analysis of Collagen Percentage

The hydroxyproline content of muscle was used to determine the collagen percentage with use of a modification of a previously published protocol[32]. Samples of tissue that were 20 to 25 mg were hydrolyzed in 6 N HCl at 110°C for eighteen hours and neutralized with NaOH to a pH of 6.98 to 7.04. The samples were then incubated with a chloramine T solution for twenty minutes at room temperature (20° to 25°), followed by the addition of a p-dimethylaminobenzaldehyde solution and incubation at 60°C for thirty minutes. Hydroxyproline concentration was determined with spectrophotometry at 550 nm and was normalized to the wet mass of the original tissue sample. Hydroxyproline standard solutions provided a calibration curve for spectrophotometry. Hydroxyproline content was used to calculate collagen amount with a constant (7.46) that corresponds to the average number of hydroxyproline residues in a collagen molecule[33].

Data Analysis

Three separate single fiber and fiber-bundle passive mechanics experiments on each sample were averaged to obtain a single value per biopsy sample. Between-muscle comparisons of fiber and bundle diameter, slack sarcomere length, elastic modulus, and titin molecular weight were made with use of three-way analysis of variance (group × muscle × size) with repeated measures for muscle and size after the data were screened for normality and homogeneity of variances. When significant differences were identified for each dependent variable, post-hoc least significant difference tests were used to identify differences between individual muscles. Linear regression was used to determine whether there were significant relationships between titin molecular weight, collagen, tear size, and single fiber as well as fiber-bundle elastic modulus. All values are reported as the mean and standard error unless otherwise noted. Statistical tests were made with use of SPSS software (version 20.0; IBM, Armonk, New York), with critical p values set to 0.05.

Source of Funding

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Results

There were no significant differences between groups in terms of age, sex, or height (Table I). In the supraspinatus tear group, two patients had a concomitant infraspinatus tear. Additionally, the duration of the shoulder symptoms was slightly longer in the supraspinatus tear group. However, this difference did not reach significance.

The structural data for the single fibers and fiber bundles indicated that the fiber bundles consisted of ten to twenty fibers, as anticipated, and their diameters and starting cross-sectional

TABLE II Data from Biopsy Samples*

	Supraspinatus		Infraspinatus	
	Intact	Torn	Intact	Torn
Diameter *(mm)*				
Single fiber	0.120 ± 0.026†	0.074 ± 0.028†	0.098 ± 0.015†	0.103 ± 0.017†
Fiber bundle	0.365 ± 0.047†	0.400 ± 0.051†‡	0.337 ± 0.055†	0.465 ± 0.060†‡
Starting cross-sectional area *(mm^2)*				
Single fiber	0.006 ± 0.001†	0.004 ± 0.001†	0.010 ± 0.004†	0.010 ± 0.004†
Fiber bundle	0.113 ± 0.030†	0.143 ± 0.033†	0.086 ± 0.027†	0.141 ± 0.030†
Slack sarcomere length *(μm)*				
Single fiber	1.96 ± 0.11	2.12 ± 0.12	2.06 ± 0.09	2.00 ± 0.10
Fiber bundle	2.09 ± 0.05	2.05 ± 0.06	2.08 ± 0.05	2.03 ± 0.06
Passive elastic modulus *(kPa)*				
Single fiber	34.09 ± 4.72†	41.67 ± 5.18†‡	39.64 ± 4.71†	25.93 ± 5.16†‡
Fiber bundle	237.41 ± 59.78†§	515.74 ± 65.48†‡§	193.71 ± 34.96†	118.67 ± 38.29†‡
Fiber titin molecular weight *(kDa)*	3703.1 ± 16.1	3708.3 ± 19.7	3685.0 ± 20.5	3730.2 ± 25.0
Fiber bundle collagen *(% wt/wt)*	10.9 ± 3.1§	19.1 ± 2.3§	11.0 ± 4.0	17.2 ± 2.9

*Values are given as the mean and standard error for three fibers or bundles per specimen from forty biopsy samples (twenty patients). †Significant difference between the single fiber and fiber-bundle data within the same muscle and injury group ($p < 0.05$). ‡Significant difference between the supraspinatus and infraspinatus single fiber or fiber-bundle data when comparing the same parameter within the torn group ($p < 0.05$). §Significant difference between the data when comparing the same muscle group between the intact and torn groups ($p < 0.05$).

areas were significantly larger than those for the single fibers (Table II). Slack sarcomere lengths were equivalent between muscles, tear groups, and size scales.

Elastic modulus values were significantly higher in fiber bundles compared with single fibers in all groups. Supraspinatus single fibers were very similar to infraspinatus single fibers in the intact group, but in the tear group supraspinatus fibers were stiffer (Fig. 2-A). For fiber bundles, the supraspinatus and infraspinatus had comparable elastic moduli. However, when the supraspinatus tendon was torn, the supraspinatus bundles became significantly stiffer than the intact bundles ($p < 0.05$) and were more than four times as stiff as the infraspinatus bundles (Fig. 2-B). There was no significant difference between the groups in titin molecular weight. However, collagen content was higher in the supraspinatus muscle when it was torn compared with when it was intact, with near significance ($p = 0.051$).

The infraspinatus muscle demonstrated a significant negative correlation between single fiber elastic modulus and titin molecular weight ($r^2 = 0.600$, $p = 0.005$) (Fig. 3-A). Although the supraspinatus muscle demonstrated the same negative trend, the regression relationship was not significant ($p = 0.134$). Importantly, the supraspinatus muscle demonstrated a

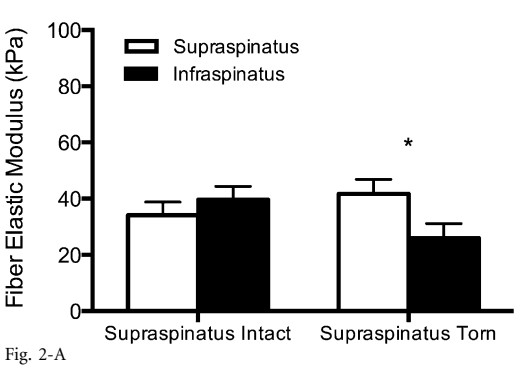

Fig. 2-A

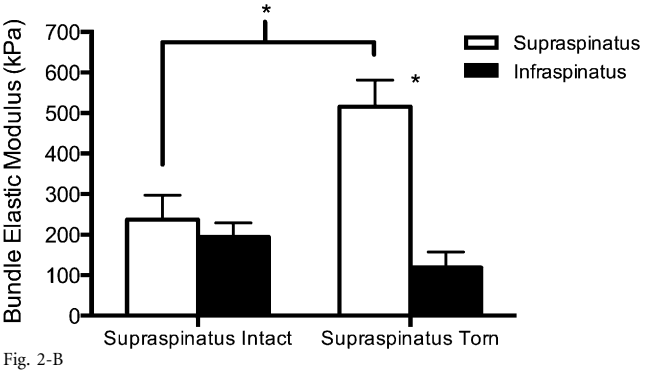

Fig. 2-B

Average single fiber (Fig. 2-A) and fiber-bundle (Fig. 2-B) elastic moduli for each muscle and tear group. These data indicated that single fiber elastic modulus decreases in the infraspinatus muscle when the supraspinatus muscle is torn. Importantly, supraspinatus muscle fiber-bundle modulus increases when the muscle is torn and becomes significantly higher than that in the infraspinatus. Asterisks indicate a significant difference ($p < 0.05$), and error bars represent the standard error of the mean.

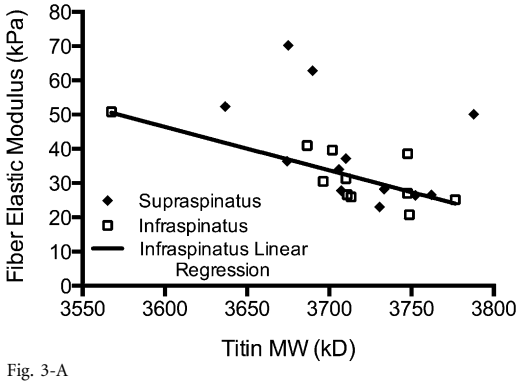

Fig. 3-A

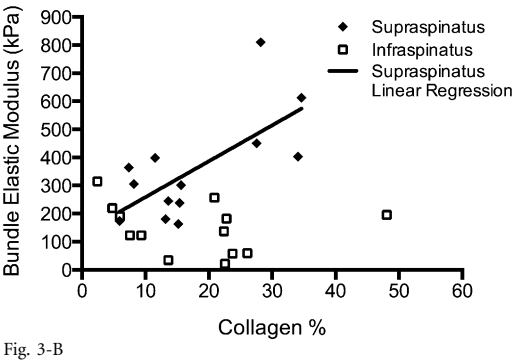

Fig. 3-B

Fig. 3-A Single fiber elastic modulus is negatively correlated with titin molecular weight (MW) in the infraspinatus muscle ($r^2 = 0.600$, $p = 0.005$). **Fig. 3-B** Fiber-bundle elastic modulus is positively correlated with collagen content in the supraspinatus muscle ($r^2 = 0.465$, $p < 0.01$).

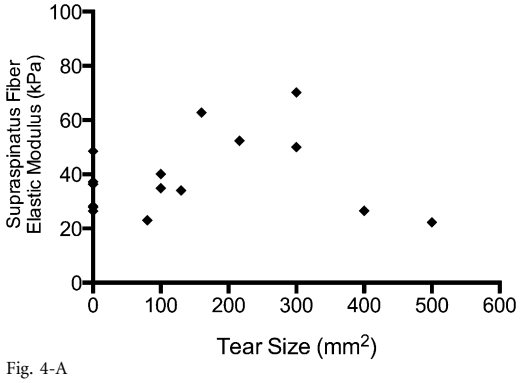

Fig. 4-A

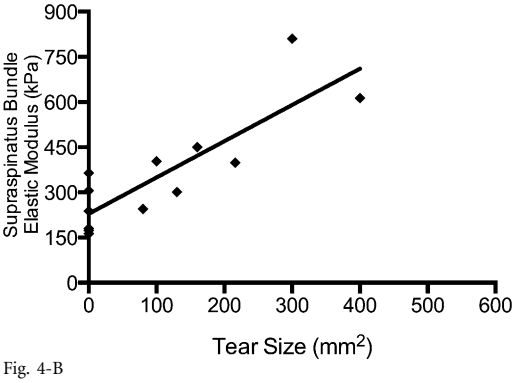

Fig. 4-B

Fig. 4-A Single fiber elastic modulus was not correlated with tear size. **Fig. 4-B** However, fiber-bundle elastic modulus had a strong positive correlation with tear size ($r^2 = 0.702$, $p < 0.001$).

significant positive correlation between fiber-bundle elastic modulus and collagen content ($r^2 = 0.465$, $p = 0.010$) (Fig. 3-B). The infraspinatus muscle demonstrated no such trend.

When supraspinatus single fiber and fiber-bundle elastic modulus was regressed against tear size, there was no relationship between the severity of the tear and the single fiber elastic modulus (Fig. 4-A), but there was a significant and strong positive correlation between the bundle elastic modulus and the tear size ($r^2 = 0.702$, $p < 0.001$) (Fig. 4-B).

Discussion

The purpose of this study was to explore the passive mechanical properties of the supraspinatus and infraspinatus muscles in intact and torn rotator cuffs. We found very small reductions in the single fiber passive elastic modulus of the infraspinatus muscle when the supraspinatus muscle was torn (Fig. 2-A). Although there were no differences in titin molecular weight between groups, there was a significant negative correlation between infraspinatus single fiber modulus values and titin molecular weight (Fig. 3-A). This is consistent with previous findings[17] demonstrating that the size (molecular weight) of the intracellular spring (titin) is inversely proportional to the elasticity of single fibers.

At the fiber-bundle level, the passive elastic modulus of the supraspinatus muscle increased when it was torn and became greater than that for the infraspinatus (Fig. 2-B). This is consistent with previous data from whole muscles in animal models of cuff tears[10,11], and from whole human muscles after tears[9]. Additionally, the authors suggested that fibrosis (collagen content) was responsible for the increased elastic modulus[9-11]; we were able to confirm this statistically, as our supraspinatus fiber-bundle modulus values were positively correlated with collagen content (Fig. 3-B). Our data also demonstrated that fiber-bundle modulus increases with the size of the tendon tear, which is consistent with clinical observations[10,13]. Importantly, these data are different from those in previous reports[18,27] at the same size scales in humans, in which the comparison was with deltoid muscles, and the analytical technique included sarcomere lengths that extended to 4.8 μm (which is dramatically longer than the 3.2-μm length observed in the neutral shoulder position[27]). This does not explain why the modulus values in our study (approximately 515 kPa) were so much higher than the values observed by those authors (90 kPa). In part, this could be because the collagen content in our study was much larger than that in their study. However, these values are difficult to compare because we used a biochemical technique and they used a histological technique.

The finding of increased passive elastic modulus when the supraspinatus muscle is torn is not surprising, given previous whole muscle data. However, determining the source of that

increased passive tension is extremely important for future treatment approaches. Previous data have suggested that muscle fibers shorten[15,16], meaning that there are fewer sarcomeres in series when supraspinatus muscles retract. The result would be increased sarcomere and fiber strain when the muscle was repaired, which would increase passive tension. Previous data have also suggested that connective tissue content increases when the muscle retracts[11], which would also increase passive tension. Together, these data suggest that structural and material changes in the muscle are responsible for elevated passive tensions at the time of repair. However, there were no data comparing intracellular contributions to passive tension. Our data suggested that single-cell passive tensions are not important when the muscle is torn, but extracellular structures (e.g., collagen) do play a vital role in this process. However, we did not explore the extracellular space exhaustively, and there may be other essential proteins involved in this process. This is an important future direction in this area; an extracellular proteomics approach and an investigation into the communication between myocytes, fibroblasts, and adipocytes could have crucial implications for how and why these cells adapt.

There are a number of limitations to this study. First, our "intact" shoulder samples were not free from abnormalities, which means that this group should not be considered normal. Second, there were very few infraspinatus muscles with torn tendons (n = 2), and these muscles were from patients with torn supraspinatus muscles. Although we did not observe any obvious differences between these two subjects and the remainder of the group, comparing the mechanical changes in torn supraspinatus muscle with torn infraspinatus tendons would be an important future area of study. Third, there is inherent selection bias in our biopsy technique, in that the surgeon (J.G.L.) was attempting to harvest muscle specifically and not connective tissue. This means that we were using the "best" tissue from the torn group, and the effect would be to minimize the differences between groups. Fourth, the site of the biopsy (1 to 2 cm proximal to the musculotendinous junction) was selected because it allowed access through the standard arthroscopic portals. It is unknown whether there are regional differences in the material and biochemical properties along the length of the muscle or if these change with disease. Finally, further biochemical testing (for proteoglycan and water contents, collagen fibril diameters, collagen types, and collagen crosslinking) could be valuable for understanding the extracellular matrix adaptations that lead to increased stiffness. The small amount of tissue obtained from the biopsies limited the number of analyses that could be performed in this study.

In conclusion, supraspinatus tendon tears induce passive mechanical changes in the supraspinatus muscle, which increases passive tension. These changes appear to originate in the extracellular space and are correlated with increases in collagen content. However, this does not mean that increased collagen content is directly responsible for the increased modulus, as it may be an indirect indicator of other protein changes or structural collagen changes such as increased fibril diameter or crosslinking.

Appendix

eA A figure showing an arthroscopic view of the supraspinatus muscle and the rongeur just before specimen harvest is available with the online version of this article as a data supplement at jbjs.org. ■

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