Contrast-enhanced ultrasound characterization of the vascularity of the rotator cuff tendon: Age- and activity-related changes in the intact asymptomatic rotator cuff

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The natural history of the blood supply to the rotator cuff and its role in the etiology of rotator cuff disease has not been definitively established. To date, there has not been an in-vivo dynamic assessment of the baseline vascularity of the asymptomatic rotator cuff. This study was designed to test the hypothesis that regional variations in supraspinatus tendon vascularity exist with an age-dependent decrease in asymptomatic individuals with intact rotator cuffs. Lipid microsphere, contrast-enhanced ultrasound shoulder examinations were done in 31 patients with a mean age of 41.5 years (range, 22-65 years). Images were obtained at baseline, after contrast administration at rest, and after contrast administration following exercise to visualize the intratendinous blood flow to the supraspinatus tendon. Qualitative and quantitative analysis was performed by determining 4 regions of interest (bursal medial, articular medial, bursal lateral, and articular lateral) with quantification and analysis software (QLAB Philips, Andover, MA) to examine each region of interest and normalize data for interpretation of the mean intensity per pixel. A statistically significant decrease in blood flow to the supraspinatus tendon with age was observed in a comparative analysis of patients aged younger than 40 and older than 40, ($P < .05$ *for all 4 zones after exercise and for the bursal medial, articular medial, and bursal lateral zones after exercise;* $P = .07$ *for the articular lateral zone after exercise). A statistically significant increase in blood flow with exercise was observed in an analysis of all patients (*$P < .001$*). The age-related decrease in the vascular supply of the tendon observed in this study is consistent with published reports demonstrating an increasing prevalence of rotator cuff pathology with age and may predispose to the development of rotator cuff tendinopathy and, ultimately, attritional tears. (J Shoulder Elbow Surg 2008;17:96S-100S.)*

As understanding of the natural history of rotator cuff disease continues to improve, epidemiologic data demonstrates the large prevalence of shoulder pain and rotator cuff pathology encountered in the general population.[3,4,9,18,19,23] Chronic rotator cuff tendinopathy and tearing has been associated with subacromial impingement and intrinsic degenerative changes, among other factors. Several authors have begun to identify processes relevant to intrinsic degenerative change through investigating the role of matrix metalloproteinase expression and tendon mechanobiology.[7,9,13,15,20,22]

Despite these advances, little is known about the contribution of vascularity to the development of rotator cuff tendinopathy. A recent study using orthogonal polarization microscopy at arthroscopy found a statistically significant decrease in microcirculation adjacent to rotator cuff lesions.[2] Historically, imaging and cadaveric studies have demonstrated an increasing prevalence of rotator cuff tears with increasing age and a region of hypovascularity at the articular surface of the distal aspect of the supraspinatus tendon.[4,9,12,15,18,19,21,23] The natural history of the blood supply to the rotator cuff and its role in the etiology of rotator cuff disease has not been definitively established.

To date, there has not been an in vivo dynamic assessment of the baseline vascularity of the asymptomatic rotator cuff. The potential role of vascularity in the pathogenesis of rotator cuff pathology may have significant implications for understanding the natural history of rotator cuff disease as well as for the development and application of surgical and biological interventions. This study was designed to test the hypothesis that regional variations in supraspinatus

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tendon vascularity exist with an age-dependent decrease in asymptomatic individuals with intact rotator cuffs.

MATERIALS AND METHODS

After obtaining Institutional Review Board approval, the study recruited 31 patients (10 men, 21 women) with a mean age of 41.5 years (range, 22-65 years). Patient numbers by decades were 20-29, 8; 30-39, 8; 40-49, 5; 50-59, 5; and 60-69, 5. Patients underwent lipid microsphere, contrast-enhanced ultrasound (Perflutren, Bristol-Meyers Squibb, N. Billerica, MA) examinations of a randomly selected shoulder. Images were obtained at baseline, after contrast administration at rest, and after contrast administration following exercise to visualize the intratendinous blood flow to the supraspinatus tendon.

Images of the supraspinatus tendon were obtained using a linear transducer operating in contrast harmonic mode and a mechanical index of 0.07. Contrast harmonic imaging is a form of nonlinear imaging that takes advantage of stimulated echoes produced by microbubble oscillations that result from resonance of the transmitted acoustic frequency.[1,5,6,8,14,17,24] The mechanical index (MI) is a measure of acoustic power. At low MI values (<0.1), bubbles will not be destroyed, so that loss of bubbles is by breakdown of the phospholipid membrane and exhalation of the gas in the lungs. At higher MI values (>1), bubbles will be destroyed. Encapsulated microbubbles, approximately 2-3 μm in size, undergo resonant oscillations when interacting with the insonating acoustic wave. These, in turn, produce higher-order oscillations (harmonics) that can be detected by a broad-band transducer.

Exclusion criteria included a history of shoulder pathology, tobacco use, or cardiovascular disease, as well as a partial-thickness rotator cuff tear exceeding 20% (as defined by tear quantification in the medial-lateral plane). Diabetes and other vascular conditions were not exclusion criteria.

A baseline scan was obtained initially to confirm an intact rotator cuff. An intravenous catheter was placed in the contralateral arm, and a 4-mL bolus of a 1:10 saline-diluted preparation of Perflutren was administered. After a 10-minute rest period, the patient participated in an exercise protocol attempting to optimally recruit the vasculature of the supraspinatus. The exercise consisted of 2 sets of 20 repetitions of forward elevation in the plane of the scapula with a 5-lb weight. A postexercise scan was then performed after the administration of an additional 4-mL bolus of the saline-diluted Perflutren preparation.

Qualitative and quantitative analysis was performed by determining 4 regions of interest (bursal medial, articular medial, bursal lateral, and articular lateral) with ultrasound imaging quantification and analysis software (QLAB, Philips, Andover, MA). A vertical line in the coronal plane passed through the rotator cuff tendon at the lateral aspect of the humeral head articular cartilage (medial aspect of the footprint) and extended superiorly to divide the cuff into medial and lateral sections. A second horizontal oblique line was then drawn in the axial plane, bisecting the tendon to divide the cuff further into bursal and articular sections (Figure 1). The bursal regions of interest included the adjacent peritendinous bursal vessels. This ultrasound imaging software permitted analysis of each region of interest and normalization of data for interpretation of the mean intensity per pixel to analyze the contrast-enhanced imaging of blood flow. Two 4-minute acquisitions were obtained, from which baseline and peak enhancement were estimated for each region of interest. Postinjection images were then normalized per patient relative to their baseline values.

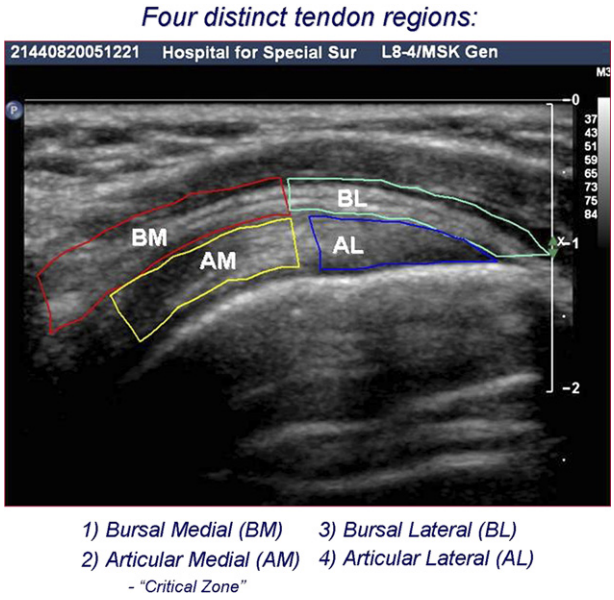

Figure 1 Regions of interest in the critical zone were the bursal medial *(BM)*, articular medial *(AM)*, bursal lateral *(BL)*, and articular lateral *(AL)*.

The data obtained were spatially averaged over several hundred pixels within each region of interest to facilitate noise reduction. A component of temporal averaging was also introduced by choosing the peak values of the trend behavior at 2 points between 1 and 3 minutes.

No patient had an adverse reaction to the contrast agent as assessed by measurement of blood pressure, heart rate, and pulse oximetry during the study and a follow-up phone call 48 hours later.

Descriptive statistical analysis consisted of means and standard deviations for continuous variables and frequency counts and percentages for discrete variables. Inferential analysis was performed using a Kruskal-Wallis nonparametric analysis of variance with post hoc Wilcoxon signed ranks nonparametric tests. Nonparametric analyses were selected because of concerns about the likelihood of nonnormal data distributions. A value of $P < .05$ was considered significant. All statistical analyses were performed using SPSS 13.0 software (SPSS Inc, Chicago, IL).

RESULTS

Regional variations in flow

A comparative analysis of blood flow differences among the 4 regions of interest demonstrated a

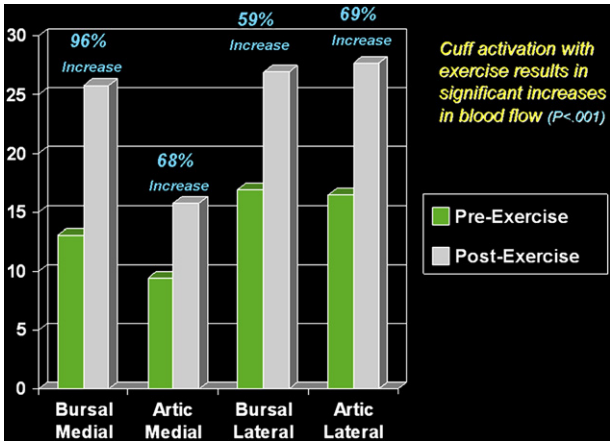

Figure 2 Result of cuff activation.

consistent region of decreased vascularity at the articular medial margin of the rotator cuff. When the results obtained from this region were compared with the other 3 regions of interest before exercise, this finding was statistically significant for comparisons with the bursal medial ($P = .002$) and lateral zones ($P = .003$) and approached statistical significance for comparison with the articular lateral zone ($P = .052$). After exercise, this analysis revealed a statistically significant decreased blood flow within the articular medial region compared with all of the other regions of interest ($P < .002$).

Effect of exercise on cuff activation

Exercise was used in this study to improve our analysis of cuff vascularity by increasing recruitment of vessels that may have potentially not been visualized at rest. This was accomplished through a standardized protocol with consistent time intervals to minimize potential sources of error in data collection and analysis. After exercise, a 59% to 96% increase in blood flow was observed ($P < .001$; Figure 2). This statistically significant increase is indicative of enhanced recruitment of available vessels and strengthens the assessment of regional flow with this contrast-enhanced technique.

Comparative analysis of blood flow in patients according to age

Data were analyzed to compare age-related flow changes by decade and according to region of interest. In a comparative analysis of patients younger and older than 40 years before exercise, a 47% to 53% decrease in blood flow was observed ($P < .05$ for the bursal medial and lateral as well as the articular medial zone; $P = 0.07$ for the bursal lateral zone; Figure 3). The results of exercise strengthened the statistical significance of this observation. In an analysis of the same groups after exercise, a 38% to 54% decrease in blood flow was observed ($P < .05$; Figure 4).

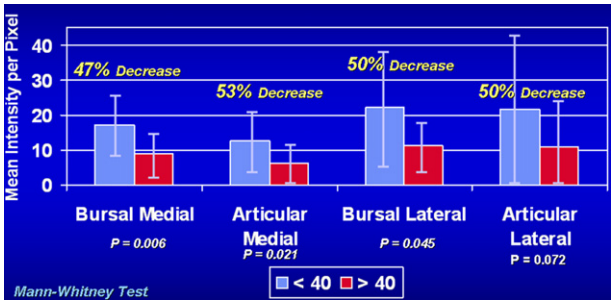

Figure 3 Comparative analysis of patients younger and older than 40 years old before exercise. Error bars show the standard deviation.

DISCUSSION

This study is the first, to our knowledge, to report an age-related decrease in the blood supply to the intact, asymptomatic rotator cuff in vivo. This novel technique of microbubble, contrast-enhanced ultrasound for musculoskeletal imaging was used to identify intratendinous blood flow in each patient and assess the baseline blood supply to the intact rotator cuff in asymptomatic subjects. The etiology of rotator cuff disease is a topic of great controversy, broad research interest, and significant clinical relevance for diagnosis, surgical indications, and operative management. Although historically the literature has defined subacromial impingement and intrinsic degenerative change as primary issues of concern, recent investigations into the etiology of rotator cuff disease have led to the identification of several other potential contributing factors. Exercise-based animal model studies indicate that repetitive mechanical loading of tendons may result in inflammation and degenerative change through both mechanical damage and biochemical mediators. Recently, the basic science literature on fibroblast and tendon mechanobiology has identified altered expression of degradative enzymes (matrix metalloproteinases 1 and 3) and increased production of inflammatory mediators in response to stretching or loading in vitro.[7,9,13,15,20] Despite these developments, it remains clear that a consideration of the vascular contribution to this process is essential.

This study has several limitations. Our sample size enabled us to show statistical significance with a nonparametric Mann-Whitney test. Our study design did not include a power analysis, however, because the novelty of this technique and its application for the assessment and quantification of intratendinous blood-flow limited our ability to perform an adequate power

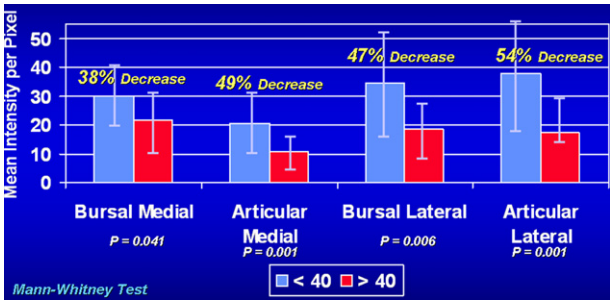

Figure 4 Comparative analysis of patients younger and older than 40 years old after exercise. Error bars show the standard deviation.

analysis. With a greater sample size, we believe the statistical significance of our data would be increased.

Lack of blinding is another limitation. The acquisition and analysis of data were performed by a single highly experienced musculoskeletal ultrasonographer. Therefore, although we believe our intersubject analysis of the data was consistent, the lack of blinding and an additional radiologist analyzing the data might potentially have introduced bias. Participants were recruited from the medical center community, and this introduced a risk of selection bias.

We chose to include patients with partial-thickness tears up to 20% of the tendon in the medial-to-lateral plane. This number was selected arbitrarily as an amount that most surgeons would believe did not categorically represent a pathologic state requiring surgical intervention.

Finally, the findings of this study are based on an assertion that peak enhancement is a function of both capillary density and regional flow.

The natural history data on rotator cuff disease demonstrates an increasing prevalence with increasing age,[3,5,7,10-12] which may imply a role for a vascular contribution to intrinsic degenerative change. Biberthaler et al[2] identified a statistically significant decrease in microcirculation adjacent to rotator cuff lesions. Several cadaver studies have examined the blood supply to the rotator cuff and identified a consistent hypovascular zone at the articular surface of the tendon as it approaches the greater tuberosity footprint.[4,9,16,18] Similarly, after exercise in this study, a statistically significant decrease in blood flow was observed within the corresponding articular medial region compared with all of the other regions of interest ($P < .002$). This finding is consistent with previous reports that have defined the hypovascular critical zone or rotator crescent in this portion of the tendon.[4,9,16,18] Some authors believe these findings may play a role in the pathogenesis of partial- and full-thickness rotator cuff tears. The role of the decreased blood supply within this region of the cuff to partial- and full-thickness rotator cuff tears is unknown and warrants further study.

In conclusion, the data presented in this study are consistent with the historical literature because the articular–medial region of interest demonstrated a consistently decreased blood supply compared with the other 3 quadrants. The findings of an age-related decrease in the blood supply to the asymptomatic, intact rotator cuff suggest a possible contributing role of vascularity in the pathogenesis of rotator cuff tendinopathy, which requires further investigation. This technique of contrast-enhanced ultrasound imaging of the rotator cuff appears to be a safe and effective tool for assessing the tendinous blood supply.

REFERENCES

1. Averkiou M, Powers J, Skyba D, Bruce M, Jensen S. Ultrasound contrast imaging research. Ultrasound Q 2003;19:27-37.
2. Biberthaler P, Wiedemann E, Nerlich A, et al. Microcirculation associated with degenerative rotator cuff lesions: in vivo assessment with orthogonal polarization spectral imaging during arthroscopy of the shoulder. J Bone Joint Surg Am 2003;85:475-80.
3. Bridges-Webb C, Britt H, Miles DA, Neary S, Charles J, Traynor V. Morbidity and treatment in general practice in Australia. Aust Fam Phys 1993;22:336-9, 342-6.
4. Brooks CH, Revell WJ, Heatley FW. A quantitative histological study of the vascularity of the rotator cuff tendon. J Bone Joint Surg Br 1992;74:151-3.
5. Chen LX, Wang XF, Nanda NC, et al. Real-time three-dimensional myocardial contrast echocardiography in assessment of myocardial perfusion defects. Chin Med J (Engl). 2004;117:337-41.
6. DePalma AF, White JB, Callery G. Degenerative lesions of the shoulder joint at various age groups which are compatible with good function. Instr Course Lect 1950;7:168-80.
7. Gimbel JA, Van Kleunen JP, Mehta S, Perry SM, Williams GR, Soslowsky LJ. Supraspinatus tendon organizational and mechanical properties in a chronic rotator cuff tear animal model. J Biomech 2004;37:739-49.
8. Kobayashi N, Yasu T, Yamada S, et al. Influence of contrast ultrasonography with perflutren lipid microspheres on microvessel injury. Circ J 2003;67:630-6.
9. Lin TW, Cardenas L, Soslowsky LJ. Biomechanics of tendon injury and repair. J Biomech. 2004;37:865-77.
10. Lohr JF, Uhthoff HK. The microvascular pattern of the supraspinatus tendon. Clin Orthop 1990;254:35-8.
11. Michener LA, McClure PW, Karduna AR. Anatomical and biomechanical mechanisms of subacromial impingement syndrome. Clin Biomech 2003;18:369-79.
12. Miniaci A, Dowdy PA, Willits KR, Vellet AD. Magnetic resonance imaging evaluation of the rotator cuff tendons in the asymptomatic shoulder. Am J Sports Med 1995;23:142-5.
13. Molloy TJ, Kemp MW, Wang Y, Murrell GA. Microarray analysis of the tendinopathic rat supraspinatus tendon: glutamate signaling and its potential role in tendon degeneration. J Appl Physiol 2006; 101:1702-9.
14. Mor-Avi V, Lang RM, Robinson KA, et al. Contrast echocardiographic quantification of regional myocardial perfusion: validation with an isolated rabbit heart model. J Am Soc Echocardiogr 1996; 9:156-65.
15. Perry SM, McIlhenny SE, Hoffman MC, Soslowsky LJ. Inflammatory and angiogenic mRNA levels are altered in a supraspinatus tendon overuse animal model. J Shoulder Elbow Surg. 2005;14(1 suppl S):79S-83S.
16. Rathbun JB, Macnab I. The microvascular pattern of the rotator cuff. J Bone Joint Surg Br 1970;52:540-53.

17. Richards PJ, Win T, Jones PW. The distribution of microvascular response in Achilles tendonopathy assessed by colour and power Doppler. Skeletal Radiol 2005;34:336-42.
18. Rothman RH, Parke WW. The vascular anatomy of the rotator cuff. Clin Orthop 1965;41:176-86.
19. Sher JS, Uribe JW, Posada A, Murphy BJ, Zlatkin MB. Abnormal findings on magnetic resonance images of asymptomatic shoulders. J Bone Joint Surg Am 1995;77:10-5.
20. Soslowsky LJ, Thomopoulos S, Esmail A, et al. Rotator cuff tendinosis in an animal model: role of extrinsic and overuse factors. Ann Biomed Eng 2002;30:1057-63.
21. Tempelhof S, Rupp S, Seil R. Age-related prevalence of rotator cuff tears in asymptomatic shoulders. J Shoulder Elbow Surg 1999;8:296-9.
22. Wang JHC, Iosifidis MI, Fu FH. Biomechanical basis for tendinopathy. Clin Orthop Relat Res 2006;443:320-32.
23. Yamaguchi K, Tetro AM, Blam O, Evanoff BA, Teefey SA, Middleton WD. Natural history of asymptomatic rotator cuff tears: a longitudinal analysis of asymptomatic tears detected sonographically. J Shoulder Elbow Surg 2001;10:199-203.
24. Zhao YZ, Luo YK, Zhang Y, Mei XG, Tang J. Property and contrast-enhancement effects of lipid ultrasound contrast agent: a preliminary experimental study. Ultrasound Med Biol 2005;31:537-43.