A major concern after rotator cuff surgery is the increasing number of reported failures in cases of large and massive tears. This failure rate has been reported to be between 38% and 65% in primary repairs. The failure of rotator cuff repairs can be attributed to many factors. First, the rotator cuff is hypovascular, which limits its ability to heal tissue damage that results from the microtrauma created through overuse and the natural aging process. The Effects of Augmentation With Swine Small Intestine Submucosa on Tendon Healing Under Tension

Histologic and Mechanical Evaluations in Sheep

Theodore F. Schlegel,*† MD, Richard J. Hawkins,‡ MD, Chad W. Lewis,§ PhD, Tatiana Motta,§ DVM, MS, and A. Simon Turner,§ BVSc, MS, Dipl. ACVS

From the †Steadman Hawkins Research Foundation, Vail, Colorado, and the ‡Department of Mechanical Engineering and §Department of Clinical Science, Colorado State University, Fort Collins, Colorado

Background: Rotator cuff failure after surgery may be attributed to inferior tissue healing properties that result from repetitive cyclic loading during early rehabilitation. Enhancing the biological healing process may reduce the incidence of failures after rotator cuff repairs.

Hypothesis: Augmentation of rotator cuff tissue using swine small intestine submucosa in a sheep model will improve the rate and quality of tissue repair.

Study Design: Controlled laboratory study.

Methods: We resected and reattached 26 sheep infraspinatus tendons under tension, with 13 animals receiving a small intestine submucosa patch (augmented group). Animals were sacrificed at 12 weeks, and biomechanical testing and histologic evaluation were performed. Biomechanical testing was completed in 10 tendons from each group. Specimens were loaded to failure at a constant displacement to obtain the load deformation curve used to calculate load to failure and stiffness of the healed bone-tendon interface. Histologic testing addressed tissue healing at the bone-tendon interface.

Results: The load-to-failure data did not indicate a significant difference between the augmented and nonaugmented groups (1252 ± 402 N vs 985 ± 459 N, respectively; P > .05). However, the augmented group had significantly better stiffness than the nonaugmented group (215 ± 44 N/mm vs 154 ± 63 N/mm, respectively; P = .03). Histologic data revealed that the infraspinatus tendon in all specimens inserted into the bone through a zone of fibrocartilage, although none of the patches were intact.

Conclusion: Although there were no differences in the load-to-failure data between the 2 groups, the statistically significant improvement in stiffness for the augmented group is clinically relevant. Stiffness is the biomechanical parameter representing the tissue response to subdestructive loads seen with early rehabilitation. Augmenting the repair with a collagen matrix improved the early healing characteristics of the repair construct.

Clinical Relevance: Enhancing the biological process of tendon healing under tension by using a collagen matrix patch may improve the ultimate success of rotator cuff repair.

Keywords: rotator cuff; collagen patch; animal model; biomechanical

*Address correspondence to Theodore F. Schlegel, MD, Steadman Hawkins Denver Clinic, 8200 East Belleview Avenue, Suite 615, Greenwood Village, CO 80111.

Presented at the 29th annual meeting of the AOSSM, San Diego, California, July 2003.

One or more of the authors has declared a potential conflict of interest: an unrestricted research grant was received from Biomet.

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tendon with poor tissue quality, creating difficulties in achieving secure fixation with our current repair techniques. Second, there may be forces generated on the tendon during the early rehabilitation process that exceed the strength of the repair. Reilly and colleagues calculated that the supraspinatus muscle generates 300 N of force as the arm is moved from 0° to 30° of abduction. This finding is of concern because several basic science studies using a sheep model have shown that the pullout strength of the repair construct at 12 weeks is significantly lower than this value.

As low loads are placed on the healing tendon during early rehabilitation, the tendon gradually pulls away from the initial repair site. This phenomenon was first described by Burkhart et al in their cyclic loading study, which showed progressive gap formation with an increasing physiological load of 180 N. As few as 25 cycles were required to create 5 mm of gap formation, whereas an average of 188 cycles were required to create a 10-mm gap, which is synonymous with a failure. Gap formation may result in an inferior repair construct, ultimately leading to failure of the rotator cuff repair, particularly in large and massive repairs.

To improve success in rotator cuff repairs, either a stronger, more secure initial construct must be developed or the healing process must be enhanced. Although advancements have been made in fixation techniques, including new suture materials, revolutionary fastening devices, and modified stitch patterns to improve holding power within the degenerative tissue, these advancements remain unproven. Even if fixation methods are improved, persistent failures may still occur, particularly in cases with limited healing potential secondary to poor tissue quality, thus leading to persistent failure of rotator cuff repairs.

This project intends to address the feasibility of tissue engineering to improve healing potential at the repair site. Previous investigators have answered some of the questions regarding the use of collagen patches in rotator cuff repairs. Using a dog model, Dejardin et al demonstrated that swine small intestine submucosa (SIS) could be used to stimulate regeneration of rotator cuff tissue when it was used to replace a completely resected infraspinatus tendon. At both 3 and 6 months, the gross appearance, histologic continuity, and failure mode of the SIS-regenerated constructs mimicked those of a sham-operated tendon and native infraspinatus tendons. Those results suggested that host tissue ingrowth and implant remodeling will occur with solid integration of the regenerated tissue to the muscular and bony interfaces. However, the ultimate strength of the SIS-regenerated tendons was significantly lower than that of the native infraspinatus tendons. Although the biomechanical properties of the replaced tissue were inferior to those of native tendons, the study suggested that tissue augmentation may be able to improve our current repair techniques.

The intention of our study was to complement the work of Dejardin et al by exploring the feasibility of tissue engineering to “augment” the repair, rather than to “fill” a defect. In a clinical setting, we would be more likely to use a collagen patch as a method of improving the healing potential of a tendon repaired under tension, rather than using it as a means of replacing a defect in a massive, irreparable repair.

It was our hypothesis that augmentation with swine SIS would improve the rate and quality of tissue healing after rotator cuff repair in a sheep model. To address this question, we compared repair techniques. We employed biomechanical and histologic analyses to evaluate the differences between the 2 repair constructs.

MATERIALS AND METHODS

Power Analysis

A prehoc power analysis at 80% power, α = .05, was performed, and it was determined that 10 sheep in each group were necessary to detect a change of 50% in load to failure and strength when comparing SIS-augmented and nonaugmented groups.

Study Groups

This study was approved by the institutional animal care and use committee at Colorado State University. A total of 26 sheep were used. With SAS software (version 8.02, SAS Institute, Cary, NC), half of the sheep (n = 13) were randomly assigned to a group in which the tendon repair construct was augmented (AC group) with a porcine small intestine submucosa patch (Biomet, Warsaw, Ind). The other half (n = 13) had an identical tendon repair performed, but the construct was not augmented (NA group). The control group was composed of contralateral limbs from sheep in the study. Ten sheep from each group were used for mechanical testing; the additional 3 animals from each group were used for histologic evaluation.

This animal model was chosen because the shape of the infraspinatus tendon in the sheep is similar to the human supraspinatus tendon in width and thickness. All animals were sacrificed at 12 weeks after repair.

Operative Technique

All sheep had two 5-mm (15 µg/h) transdermal analgesic patches (Duragesic, Janssen Pharmaceutic, Titusville, NJ) applied preoperatively to the lateral thoracic region and received antibiotic coverage (cefaclor sodium; Ancef 1 g preoperatively, 1 g intraoperatively, and 1 g postoperatively). General anesthesia was induced with ketamine (4 mg/kg) and Valium (7.5 mg total) and maintained on isoflurane (1.5% in 100% oxygen, 2 L/min). With the sheep in the left lateral recumbent position, the right shoulder was shaved, and the surgical site was prepared for aseptic surgery using alternating scrubs of povidone-iodine...
(Betadine, Purdue-Frederick, Norwalk, Conn) and alcohol. After the surgical site was steriley draped, a 12-cm incision was made over the right shoulder joint. The subcutaneous colli muscle and brachial fascia were divided in line with the incision. The plane of dissection was established along the cranial border of the acromial head of the deltoide muscle. The insertion of the infraspinatus tendon was then isolated. The tendon was sharply detached from the greater tuberosity of the humerus, and 5 mm of the distal tendon was resected before reattachment to simulate a rotator cuff repair being performed under tension.

A bone trough, 2.0 cm in length and 0.5 cm in depth, was prepared in the proximal humerus using an osteotome and burr. Four separate tunnels were created in the greater tuberosity using the Linvatec shoulder set (Linvatec Corp, Largo, Fla). The infraspinatus tendon was sutured into the trough using three No. 2 nonabsorbable sutures (Ethibond, Ethicon Inc, Somerville, NJ) in a modified Mason-Allen stitch. Each limb of the suture was passed through a separate osseous tunnel, with the 2 center tunnels being used twice. The sutures were tied over a cortical bridge.

Before implantation in the AC group, the SIS device was rehydrated for 2 minutes in normal saline solution at room temperature. A 10 × 20-mm patch of SIS was placed on the superficial aspect of the repaired tissue. The initial fixation of the patch was achieved by using a free No. 5 Mayo needle to pass the free ends of the 2 central limbs of the nonabsorbable suture used in the transosseous repair of the infraspinatus tendon, eventually tying these ends over the patch. The implant was sutured to the surrounding tissues using simple 2-0 polydioxanone sutures. Once the repair was completed, the surgical site was lavaged with sterile saline solution. The brachial fascia and subcutaneous tissue were closed as separate layers using 2-0-polyglycolic acid and nylon (Dermalon, Ethicon Inc) for the skin.

**Postoperative Care**

After surgery, assessment of pain was recorded daily in all sheep. The animals were placed in a small pen for the first 6 weeks to limit activities. After 6 weeks, the sheep were turned into a large pen (with access to a 3-sided shelter) for the remainder of their convalescence and were allowed unrestricted activities.

**Sample Preparation**

At 12 weeks postoperatively, the sheep were sacrificed in a humane manner using an intravenous overdose of barbiturate. At necropsy for all animals, each infraspinatus muscle-tendon complex and its corresponding humerus were dissected from the operated shoulder and visually examined grossly. Observations were made as to the healing of the tendon and the condition of the surrounding tissue.

**Histologic Evaluation**

Three animals from each group were used for histologic evaluation. Both the augmented and nonaugmented tendons, along with a contralateral control tendon, were harvested en bloc from just proximal to the musculotendinous junction to the greater tuberosity. The specimens were fixed in 10% neutral buffered formalin and decalified with EDTA. Five 10-µm sections were obtained from the insertion (repair) site of the decalcified sections, and the sections were stained with hematoxylin and eosin (H&E). All histologic sections were examined under light and polarized light microscopy. The pathologist was blinded to the treatment groups.

**Biomechanical Testing**

In the remaining 10 sheep from each treatment group, the infraspinatus muscle-tendon complex and the humerus were isolated from the operated and control (contralateral) shoulders. The harvested specimens were wrapped in saline-soaked gauze sponges and frozen at −80°C until mechanical testing was performed. Before testing, the specimens were thawed in normal saline bath at 37°C. All soft tissues, with the exception of the superficial head of the infraspinatus, were carefully removed from the specimen. The humeral diaphysis was embedded in a low-temperature thermostat resin (Dyna-Cast, Cleveland, Ohio) and secured to a custom-designed loading fixture. The upper grip was clamped to the infraspinatus tendon using a custom-made cryogenic vise frozen with CO₂ to −25°C ± 5°C.

The scapula was anatomically aligned, and the end of each specimen was potted in polymethyl methacrylate (PMMA). The specimens were subjected to biomechanical testing using the MTS 809 Axial/Torsion Test System (MTS Systems Corp, Eden Prairie, Minn). The sutures on the lateral aspect of the humerus were not cut, and the specimens were kept moist throughout the testing procedure. The clamps maintained anatomical alignment and ensured that the force vector direction was along the anatomical line of application.

Before testing, a cyclic preload of 5 N was applied to each specimen for 5 cycles. The specimens were then loaded to failure at a constant displacement rate of 500 mm/min until failure. The load deformation curve was digitally recorded and used to calculate the energy to failure, and the slope of the linear portion of the force displacement curve was used to determine the peak stiffness of the healed bone-tendon interface. The mode of failure (soft tissue or insertion site) was documented.

**Statistical Analysis**

Statistical analysis was applied to establish the mean, standard error, and standard deviation of both the tensile force needed to disrupt the tendon and the stiffness of each construct. The significance of the magnitude of the differences between the experimental groups with regard to mean tensile force and stiffness was assessed using a 1-way analysis of variance and Tukey test (α = .05).

**RESULTS**

Load to failure (in newtons) and stiffness (in newtons per millimeter) were determined for both treatment groups...
without evidence of any foreign body reaction (Figure 3). In the AC group, remnants of the SIS patch were seen when the bone trough was filled with disorganized fibrous tissue. The defect induced the ability of the repair construct to resist a onetime destructive force, which is rarely seen in a clinical setting. Stiffness data are a more relevant evaluation of the mate strength of the SIS-regenerated tendons was significantly lower than that of a normal control. The results of this basic science study were encouraging, but clinically one needs to be cautious when considering this technique as an option for replacing tissue in irreparable rotator cuff tears.

As opposed to the study by Dejardin et al, in which they used the collagen matrix to replace a large defect, we believed that the SIS patch was better suited to supplement tissue healing. In the current study, we have shown that early healing is improved by supplementing the repair with the SIS patch, as compared with the same surgical technique without supplementation. There was not a significant difference in load to failure between the 2 experimental groups; however, there was a statistically significant difference in stiffness between the AC and NA groups, with the augmented specimens closer approximating the stiffness of the normal controls.

Clinically, the stiffness data are more relevant than the load-to-failure results when assessing soft tissue healing to bone. A load-to-failure measurement represents the ability of the repair construct to resist a onetime destructive force, which is rarely seen in a clinical setting. Stiffness data are a more relevant evaluation of the

**TABLE 1**  
Load to Failure and Stiffness for Augmented, Nonaugmented, and Control Tendons (means ± SDs)

<table>
<thead>
<tr>
<th>Group</th>
<th>Load to Failure, N</th>
<th>Stiffness, N/mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonaugmented</td>
<td>985.3 ± 458.9</td>
<td>155.0 ± 62.5</td>
</tr>
<tr>
<td>Augmented</td>
<td>1251.7 ± 401.7</td>
<td>215.5 ± 44.0</td>
</tr>
<tr>
<td>Control</td>
<td>5233.0 ± 736.1</td>
<td>544.5 ± 47.2</td>
</tr>
</tbody>
</table>

*Significantly different from control values.  
Significantly higher stiffness in the augmented group compared to the nonaugmented group.

![Figure 1](image1.png)  
**Figure 1.** Mean load to failure in the augmented repair (AC) and nonaugmented repair (NA) tendons. The dashed line indicates the mean load-to-failure value for the control tendons. *Significant difference in load to failure between the control and experimental groups.

![Figure 2](image2.png)  
**Figure 2.** Mean stiffness in the augmented repair (AC) and nonaugmented repair (NA) tendons. The dashed line indicates the mean stiffness value for the control tendons. *Significant difference in stiffness between the control and experimental groups. **Significantly higher stiffness in the AC group compared to the NA group.

**DISCUSSION**

Failure of rotator cuff repairs can be attributed to multiple factors relating to tendon healing, including poor tissue quality, size of the defect, and forces generated during the early rehabilitation process. To reduce repair failures, improvements in tendon healing need to be addressed. Biological enhancement of the healing process is one potential arena that, if altered, could enhance tendon healing to bone and prevent repair failures.

Recent research has documented the ability of an SIS collagen matrix to help create a cellular response to promote healing. Using a dog model, Dejardin et al showed that a porcine SIS patch could be used to stimulate regeneration of a completely resected infraspinatus tendon. Although the gross and histologic appearance of the tissue mimicked that of a native infraspinatus tendon, the ultimate strength of the SIS-regenerated tendons was significantly lower than that of a normal control. The results of this basic science study were encouraging, but clinically one needs to be cautious when considering this technique as an option for replacing tissue in irreparable rotator cuff tears.

At 12 weeks, the mean load to failure was 1252 ± 402 N for the AC group, 985 ± 459 N for the NA group, and 5233 ± 736 N for the control group (Figure 1). There was not a significant difference between the treatment groups for load to failure. A statistically significant difference did exist between the control and AC groups (P < .001) and between the control and NA groups (P < .001).

The mean stiffness for the AC group was 215 ± 44 N/mm; it was 155 ± 63 N/mm for the NA group and 545 ± 48 N/mm for the control group (Figure 2). There was a statistically significant difference between the 2 treatment groups (P = .030) and between each experimental group and the control group (P < .001).

The histologic findings were similar between the 2 treatment groups. There were no clear differences in appearance between the AC group and the NA group. The SIS patch was not fully intact in any of the augmented specimens. The augmented construct had limited inflammatory response around the graft site, and the nonaugmented specimens showed no indication of inflammatory response. Both constructs showed evidence of gap formation as the tendon healed medial to the original repair site. The defect created from where the tendon had been pulled away from the bone trough was filled with disorganized fibrous tissue. In the AC group, remnants of the SIS patch were seen without evidence of any foreign body reaction (Figure 3).
day-to-day response of the repair construct to subdestructive loads frequently seen with the rehabilitation process. Because we are trying to avoid “gapping” at the repair site, we want tissue that can resist displacement at these subdestructive loads.

The improved early healing may be due to the fibrous tissue seen filling the “gap” at the repair site in the augmented specimens. In this group, remnants of the collagen matrix could often be seen overlying the repair site. However, none of the SIS patches were found to be intact. It is our opinion that the collagen matrix was capable of inducing an early healing response before disruption of the patch, thereby improving tissue characteristics, as revealed in increased stiffness values.

Both experimental groups had significantly lower load to failure and stiffness measurements when compared with the normal controls. At 12 weeks after repair, it would be unreasonable to expect the repaired tendon to reach the strength of the contralateral tendon, as multiple studies have had similar results when comparing repairs to native control groups. France et al,\(^4\) using a cadaveric model, reported that the intact tendons were 2 to 3 times stronger than repaired tendons when testing various fixation techniques for load to failure. Dejardin et al\(^2\) also indicated that the SIS-regenerated tendons had significantly lower strengths than those of native tendons. It was not the intention of this study to determine if repairs augmented with the SIS patch would reach levels comparable to the normal control tendons. Instead, the intent was to compare the current standard repair technique to the same technique supplemented with the SIS patch.

Our study design also differs from the Dejardin et al study\(^2\) with regard to duration. Our purpose was to evaluate early tendon healing, not to address tendon healing over time. In a pilot study, we found that rotator cuff repairs had healed to nearly 25% of the strength of the control tendons at 12 weeks. Although it does not represent complete healing, we believe that using the 12-week period is sufficient to address early failure of rotator cuff repair.\(^1\)\(^2\)

With the sheep model, there were several limitations. First, although previous work has shown that the sheep infraspinatus tendon has similar mechanical properties to the human supraspinatus tendon, this model remains an approximation of the human condition. Second, given that the shoulder is a weightbearing joint in the sheep, it is likely that the loads faced in this model are significantly higher than those in humans. We had considered immobilizing the sheep after the procedure. Gerber et al\(^9\) found that a majority of cuff repairs in sheep without prevention of full weightbearing failed, regardless of the technique that was used. For this reason, he thought that the only way to protect the repair was to suspend the animal in a hanging device as well as to place a softball under the hoof of the involved limb. However, the animal care and use committee would not allow us to suspend the animal as part of an immobilization technique.

We have previously evaluated the necessity of immobilization in long-term healing of tendon repairs in a sheep model.\(^1\)\(^2\) It was found that, at 26 weeks, there was not a significant difference between the immobilized and non-immobilized treatment groups. The bone-tendon interface was similar to normal tendon load-to-failure and stiffness values, suggesting that strict restriction may not be a critical component for this model.

Regardless of the limitations, we believe that the results of our current study are valid, as we are comparing 2 groups of sheep that underwent identical surgical reattachment of the rotator cuff and identical rehabilitation programs, with the collagen patch supplementing the repair in one of the groups.
At this point, it is difficult to determine if the increase in stiffness seen with the SIS patch augmentation is clinically significant. Both the augmented and nonaugmented repairs did demonstrate gapping. Although this result is a concern, it is not unexpected, as current repair methods demonstrate healing with tendon gapping. However, our current goal is to limit this process and to improve the tissue quality at the repair site. For this reason, we still believe that the SIS patch is a viable option for enhancing rotator cuff repair. The sheep model is intended to be the first step in examining the potential ability of the SIS patch to improve tendon healing. Multicenter clinical trials examining the outcomes in patients undergoing rotator cuff repairs with and without augmentation using the SIS patch would be much more indicative of its ability to prevent failure of rotator cuff repairs in humans.

ACKNOWLEDGMENT

The authors are grateful for assistance in mechanical testing and data analysis by Jason Craig and for the technical assistance of Laura Kaufman, Patrick Siparsky, Tyler Richardson, Jenna Godfrey, and Donna Wheeler.

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