

Rotator Cuff Tears: What have we learned from animal models?

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Abstract

Rotator cuff tendon tears are among the most common soft tissue injuries that occur at the shoulder. Despite advancements in surgical repair techniques, rotator cuff repairs experience a high rate of failure. The common occurrence of tears and the frequency of re-tears require a further understanding of the mechanisms associated with injuries, healing, and regeneration of the rotator cuff. This paper reviews *in vivo* studies using the various animal shoulder models of the rat, rabbit, sheep, canine, and primate. These animal models have been used to study intrinsic and extrinsic factors leading to shoulder degeneration, various suture techniques, effects of post-surgical treatment, numerous biologic and synthetic scaffolds, and an assortment of biologic augmentations used to accelerate healing. These effects can be examined in a controlled manner using animal models without other confounding factors that sometimes limit clinical studies. The clinically impactful results will be explained to highlight the specific knowledge gained from using animal models in rotator cuff research.

Keywords: Animal Model, Rotator Cuff, Tendon Healing

Introduction

Musculoskeletal injuries and conditions affect over 28 million Americans every year costing an estimated \$254 billion¹. These injuries mainly involve soft tissues, including tendon, ligament, muscle, nerve, and cartilage. Rotator cuff tendon tears are among the most common soft tissue injuries that occur at the shoulder². The rotator cuff tendons function to provide dynamic stability to the inherently unstable glenohumeral joint³⁻⁵. This functional role, in combination with other factors, often leads to degenerative tears, particularly in older patients^{4,6}. Approximately 25-50% of asymptomatic individuals over the age of 50 have a rotator cuff tear^{7,8}. Even with the advanced approaches to rotator cuff repairs, the rate of failures and re-tears are estimated to be at 70%⁹.

This review focuses on *in vivo* animal model research that has been useful in furthering our understanding of injuries,

healing, and regeneration of the rotator cuff. We will review the animal models commonly used in rotator cuff research and explain their relevance to the human condition.

A systematic approach, evaluating over thirty animals, used specific criteria relating shoulder anatomy and function to the human to determine the rat as an appropriate model to study many aspects of the rotator cuff¹⁰. These criteria included: shoulder musculature of the rotator cuff, deltoid, and biceps; bony anatomy including the acromion, clavicle, coracoid, and humerus; articulations; and motions such as elevations and rotations. Only the rat had a prominent supraspinatus tendon which passes under an enclosed arch, similar to that of the human supraspinatus tendon (Figure 1)¹⁰. The rat is also an appropriate animal model for studying a wide range of rotator cuff pathologies because defects made to the rat rotator cuff result in inferior biomechanical and other properties¹¹. It has been used to study both intrinsic and extrinsic mechanisms of injury, the effects of overuse, passive motion, and rehabilitation.

The rabbit model has been used to examine muscular changes associated with rotator cuff tears, including muscle atrophy, twitch tension, fatigue index, and the discharge of mechanosensitive afferent units. It has also been used to study rotator cuff healing with and without scaffold augmentation. Commonly, the supraspinatus or infraspinatus has been used, however, more recent studies have proposed the use of the subscapularis due to this tendon passing under an enclosed arch¹².

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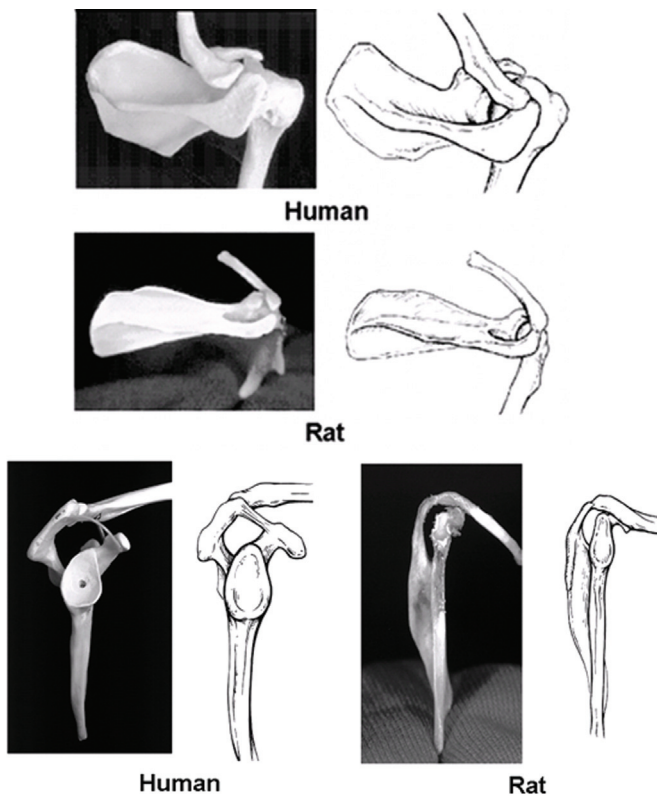


Figure 1. Comparison of human and rat shoulder bony anatomy from posterosuperior and outlet view demonstrating an enclosed arch over the supraspinatus tendon area in both cases, similar to the human. (Reprinted from Soslowky LJ, Carpenter JE, DeBano CM, Banerji I, Moalli MR. *Development and use of an animal model for investigations on rotator cuff disease. J Shoulder Elbow Surg* 1996;5:383-92, with permission from Elsevier).

Additionally, the rabbit subscapularis muscle experiences fatty infiltration after tendon detachment, similar to the human¹³.

Rotator cuff tears seen clinically are often large and chronic in nature, making the sheep an interesting model for studying the *in vivo* effects of chronic rotator cuff tears and various suturing techniques to minimize repair failure. In addition, this model has been used to study the associated muscular changes that occur with chronic cuff tears¹⁴. Unlike the rat, the sheep's anatomy is not comparable to the human. However, the sheep's infraspinatus has been described as similar to the human supraspinatus and its similar size allows for certain studies¹⁵.

The canine shoulder model has been used to study the effects of rotator cuff tendon augmentation with a variety of scaffolds^{16,17}. The canine model can produce loads to the rotator cuff that are comparable in magnitude to those experienced by the human during daily activities. This provides a useful model for the study of tendon repair augmentations. The anatomy of the canine shoulder is similar to the sheep and the infraspinatus tendon is used.

Many of the non-human primates have very similar shoulder anatomy and function to the human. However, the primate

has only been used in one recent *in vivo* study of rotator cuff tears and healing¹⁸. This is most likely due to the large cost, complexities, facilities, and management difficulties required to maintain primates in sufficient numbers for such purposes.

Native properties at the tendon insertion

An understanding of the native rotator cuff is crucial to recognize pathologic changes that occur to the tendon insertion site.

The unique structure of the tendon insertion site has been related to specific localized gene expression during development. Tenomodulin (Tnmd) and Chondromodulin-1 (Chm1) are homologous angiogenesis inhibitors that are predominantly expressed in the avascular region of tendons and cartilage. A study in young rabbits identified a population of cells that did not express either Tnmd or Chm1 between cell populations of tenocytes and chondrocytes. These cells may contribute to the enthesis formation in a mature tendon¹⁹.

The transitional zone in the mature, native enthesis is characterized by a linear decrease in the degree of mineralization across the tendon-to-bone insertion. This finding has important clinical implications because the mineral gradation may explain the high loads the rotator cuff enthesis can sustain by increasing tendon stiffness, and recreating a mineral gradation may be necessary to optimize tendon healing²⁰.

Biological and biomechanical properties of the mature, native enthesis of the supraspinatus tendon insertion site have been evaluated in the rat model²¹. Peak strain and viscoelastic properties were found to be significantly increased at the tendon end compared to the bone end of the insertion site. Collagen orientation also varied with location, demonstrating more oriented fibers at the tendon end compared to at the bone end. Additionally, collagen types II, IX, and X and aggrecan were located only at the bony end, while biglycan and decorin were localized only at the tendon end.

Pathomechanics

Intrinsic and extrinsic mechanisms have been theorized to cause rotator cuff tendon injury and tears. The rat model has been used to further enhance our understanding of these potential mechanisms of injury to the rotator cuff¹⁰.

Research examining tendon pathology caused by intrinsic stimulants has been used to investigate causes of spontaneous tendon degeneration. Changes observed after intrinsic degeneration caused by an intratendinous injection of collagenase included increased cellularity, more round metabolically active fibroblasts, and collagen disorganization¹⁰.

Corticosteroid injections are commonly given in the clinical setting to alleviate pain in the rotator cuff. The negative effect of steroid injections was reaffirmed in the rat model²²⁻²⁴, which demonstrated that a steroid injection initiates a short-term response equivalent in damage to a structural injury²⁵.

Alterations in the bone mineral density of the specific mineral gradient of the enthesis may also play a role in rotator cuff injury or tears. It was found in the rat model that increased bone mineral density enhanced failure load indicating the im-

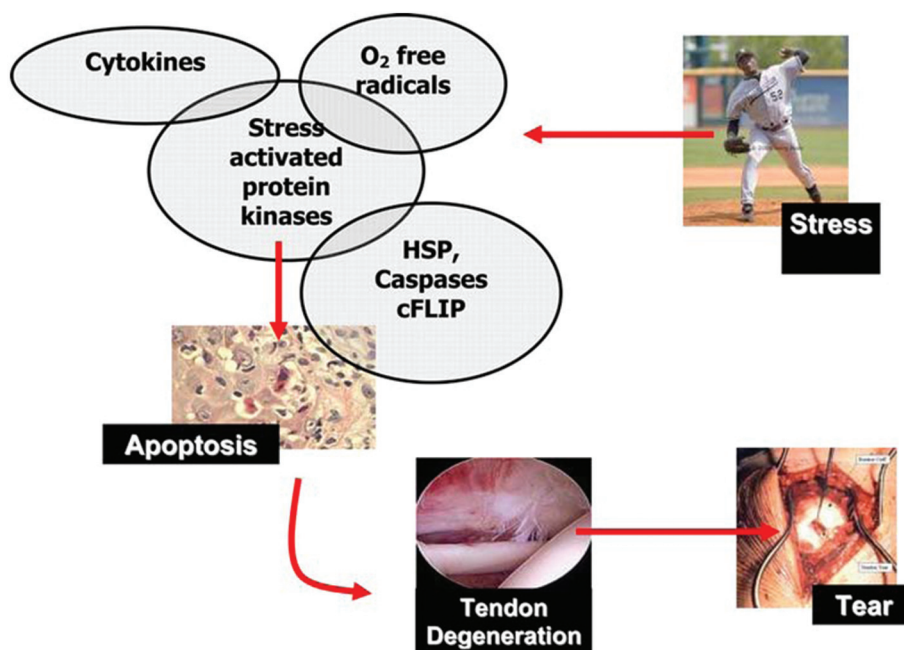


Figure 2. A theoretical paradigm linking mechanical stress to tendon degeneration via cytokines, protein kinases, oxygen free radicals, and apoptotic mediators which can be studied in animal models. (Reprinted with kind permission of Springer Science and Business Media from Millar NL, Wei AQ, Molloy TJ, Bonar F, Murrell GA. Heat shock protein and apoptosis in supraspinatus tendinopathy. Clin Orthop Relat Res 2008;466-7:1569-76).

portance of bony density in rotator cuff tears²⁶.

Rotator cuff pathology has also been theorized to originate from, or become exacerbated by, extrinsic factors such as subacromial impingement. Impingement was experimentally created by surgically attaching an Achilles tendon allograft under the surface of the acromion process which reduced the subacromial space¹⁰. The alterations observed were smaller than those due to collagenase injection. However, a combination of intrinsic and extrinsic factors resulted in persistent damage, greater than the changes due to either factor alone. The effects of subacromial impingement have also been evaluated in a rat model by implantation of bony transplants under the acromion, resulting in bursal side tendon tears²⁷.

Overuse injuries of the rotator cuff are common and have been modeled using the rat. Supraspinatus tendon mechanical properties were decreased, histology demonstrated clear degeneration²⁸ and several angiogenic and inflammatory markers were found in the supraspinatus after overuse. Further, the tendon also highly expressed cartilage markers, heat shock proteins, and markers of apoptosis²⁹⁻³². Although exact mechanisms remain elusive, there is a theoretical paradigm linking mechanical stress to apoptosis (Figure 2).

It is commonly accepted that rotator cuff tears are multifactorial, likely occurring from a combination of the described mechanisms. When overuse was combined with subacromial impingement in a rat study, it was found that the combination caused more tendon degradation (increased cross sectional area, decreased max stress and modulus) compared to either of the stimuli alone (Figure 3)³³. This provides a controlled and mechanistic approach for evaluating the various theories that exist for the pathomechanics of cuff tears.

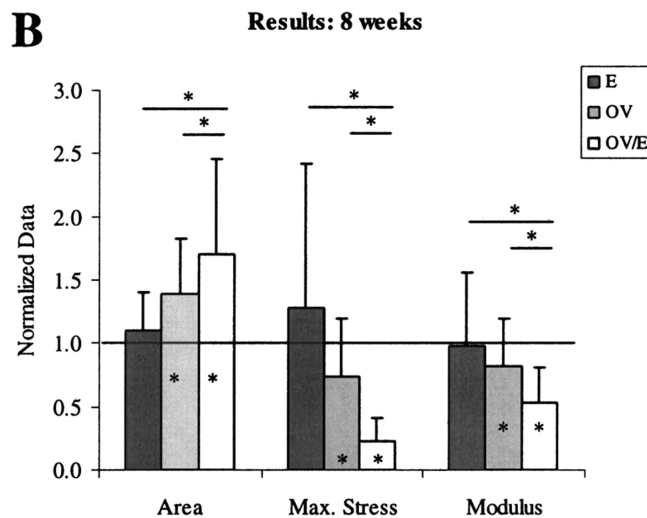


Figure 3. Overuse in conjunction with extrinsic compression (OVE) results in greater tissue damage than either stimulus alone (OV and E) in a rat model, demonstrating the multifactorial nature of rotator cuff injuries. (Reprinted with kind permission of Springer Science and Business Media from Soslowsky LJ, Thomopoulos S, Esmail A, Flanagan CL, Iannotti JP, Williamson JD 3rd, Carpenter JE. Rotator cuff tendinosis in an animal model: role of extrinsic and overuse factors. Ann Biomed Eng 2002;30-8:1057-63).

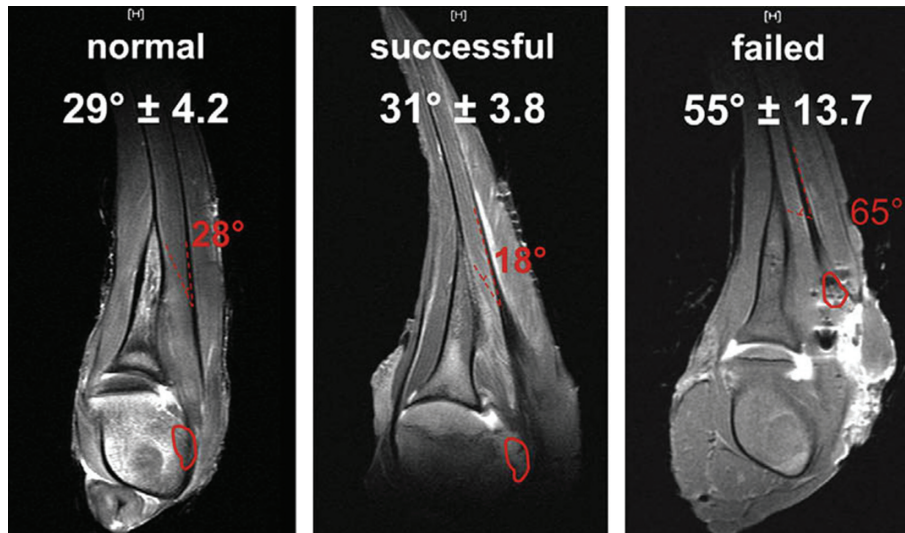


Figure 4. Magnetic resonance images depicting pennation angles of uninjured control rotator cuff, successful, and failed surgical repair of chronic infraspinatus tears in a sheep model. (Reprinted from, *J Shoulder Elbow Surg*, 18-2, Gerber C, Meyer DC, Frey E, von Rechenberg B, Hoppeler H, Frigg R, Jost B, Zumstein MA. *Neer Award 2007: Reversion of structural muscle changes caused by chronic rotator cuff tears using continuous musculotendinous traction. An experimental study in sheep*, 163-71, 2009, with permission from Elsevier).

Alterations associated with rotator cuff tears

A rotator cuff tear that goes untreated commonly leads to associated alterations or injuries of the surrounding tissues. This is commonly observed in the long head of the biceps tendon for example, which develops a variety of lesions ranging from tendinitis to complete tears. Alterations to the biceps have been observed in the rat model, mimicking the clinical observations seen in human rotator cuff tears. Specifically, biceps mechanical properties decreased with both rotator cuff tear size and time³⁴. Regional decreases in the mechanical properties along the length of the biceps after a combination of rotator cuff tears and increased loading were also noted³⁵. These results demonstrate the specific tissue changes that occur in the biceps after rotator cuff tears and may lead to more effective treatment options for patients.

When the rotator cuff is not surgically repaired after a complete tear, it loses its ability to function and transfer force created in the muscle to the humerus. This inability to transfer force alters the structure and composition of the tendon resulting in potential difficulties for tendon healing. The rabbit, rat, and sheep animal models have been used to examine the alterations to the rotator cuff tendon after a chronic detachment. Specifically, the mechanical properties of the torn tendons initially decrease and then increase at later healing times³⁶. Similar findings were observed in massive rotator cuff tears, defined as detachment of both the supraspinatus and infraspinatus tendons³⁷. When examining the composition and biochemistry of the torn tendon, alterations were found in the expressions of several extracellular matrix (ECM) proteins (collagen I, II, III, XII, aggrecan, and sulfated GAGs) and genes (IL-1 β , cyclooxygenase-2, prostaglandin E2, MMP-13,

MMP-3, and TIMP-2)³⁸, representing a continual degradation of the remaining tendon. When attempting to repair the chronic rotator cuff tear, the mechanical properties were found to slightly improve but remained inferior to controls^{14,39-41}.

In addition to studying the torn tendon, research has examined the remaining intact rotator cuff tendons after a tear. It was found that they had decreased mechanical properties and increased cross sectional area after a variety of tear situations⁴². This demonstrates that after a rotator cuff tear, the stabilizing loads of the shoulder are distributed to the remaining tendons resulting in increased stress to the otherwise healthy tendons.

The rotator cuff muscles also go through several adaptations after rotator cuff tears and repairs. One observed alteration, muscle atrophy, is also observed in the rat and sheep model, which is potentially caused by the muscle's inability to produce tension^{14,39,43,44}. In conjunction with muscle atrophy, functional characteristics such as reduced force, power, and fatigue have been seen in both a rabbit and sheep model after cuff tears^{39,45,46}. Structural changes of the muscle have also been identified in rabbits, rats, and sheep including decreased sarcomere length, pennation angle, fiber length, and fiber diameter^{44,47,48}. The structural changes of the muscle likely dictate the decreased functional characteristics after cuff tears.

Fatty infiltration of the rotator cuff muscle is a common clinical occurrence with chronic tears which has been reproduced in animal models including the sheep, rabbit, and rat^{14,39,48-51}. The models determined that fatty infiltration worsens over time⁵² and progresses proximal to distal within the muscle⁵³. When repairing a chronically torn rotator cuff, the progression of fatty infiltration did stop but did not reverse or return to control levels after repair^{39,50,54}.

Since the tension required to repair a chronically torn tendon back to the greater tuberosity can reach high levels⁵⁵ and rapid stretching of shortened muscle can cause fibrosis^{56,57}, a traction device was developed to progressively lengthen the tendon in a chronic sheep model. Muscle atrophy decreased and the penetration angle improved after successful traction and tendon repair (Figure 4). Similar to previous research, fatty infiltration of the muscle remained unchanged after traction and repair; however, it did stop progressing⁴⁴.

A complete rotator cuff tendon injury has many characteristics similar to that of an isolated neural injury¹². The rabbit model has been extensively used to study the relationship between nerve injury and cuff pathology. An experimentally induced acute inflammation had an excitatory and sensitizing effect on the mechanosensitive afferent units in the rotator cuff⁵⁸. Electrophysiologic experiments found a high density of nociceptors in the infraspinatus insertion site and muscle⁵⁹. A study using the rabbit subscapularis muscle found that a complete tenotomy resulted in muscular changes similar to those seen with denervation of the muscle, suggesting that chronic rotator cuff tears may induce neurologic damage¹³.

Tendon to bone healing

The high re-tear rate seen clinically following cuff repair is due to lack of a strong tendon to bone integration. In a reattached rabbit supraspinatus tendon, formation of a new enthesis was accompanied by extensive non-chondrocytic proliferation, followed by the appearance of chondrocytes and eventual improvements in ECM reformation, correct spatial alignment of collagen fibers, and recovery of the surgical construct strength⁶⁰ over extended time which may prohibit early rehabilitation⁶¹. Additionally, delaying repair of the supraspinatus by up to 12 weeks did not impair this enthesis reformation⁶².

Cells in surrounding tissues can be important in the repair process. In the rabbit supraspinatus tendon repair, increased cellularity was observed in the underlying bone, and the thickness of the subacromial bursa was also increased compared to control. Meanwhile, the cellularity of the tendon stump was significantly decreased. In the clinical setting, the cell source of the subacromial bursa could be important in the healing process⁶³. Similarly, the epitenon has been noted to be a source of healing⁶⁴ and this should be considered clinically.

The normal characteristics of rotator cuff healing are required to examine surgical and rehabilitation techniques that are developed to improve tendon to bone healing. A primate model was used to examine the properties of tendon healing. Histology was examined at 12 weeks post repair and demonstrated an integration of collagen fibers into the bone¹⁸. When examining the biology of the healing rotator cuff tendon in both the rabbit and rat model, several ECM proteins, growth factors, and degradation factors are temporally expressed (col1, col3, TGF β 1, TGF β 3, bFGF, bmp-12, bmp-13, bmp-14, COMP, CTGF, PDGF-bb, MMP-2, and TIMPS) demonstrating the complex interactions that are required to heal the tendon back to bone⁶⁵⁻⁶⁹.

Rehabilitation is commonly used to augment the treatment

of rotator cuff injuries. It is designed to optimize the body's natural healing ability. Overuse is a common mechanism of injury, however little scientific evidence exists evaluating treatments. Supraspinatus tendons in rats recovered from the molecular and biological effects of 4 weeks of overuse activity in as little as 2 weeks⁷⁰. This demonstrates that rest can heal tissue damage caused by overuse activity, at least in the case of a short period of overuse.

Joint immobilization is commonly used after surgical repair to protect the repaired structures until adequate strength is obtained. Longer durations of immobilization (16 weeks) in the rat improve the strength, organization, and composition of insertion site healing^{71,72}. Conversely, shorter durations of immobilization (4 and 6 weeks) in rat and sheep rotator cuff repair models do not result in improvements in insertion site healing⁷¹⁻⁷³. Although long periods of joint immobilization benefit rotator cuff insertion site healing, immobilization has also been linked to increased joint stiffness and a decreased range of motion. However, increased joint stiffness and decreased range of motion resolves 8 weeks after remobilization⁷⁴. In addition, exercise following 2 weeks of immobilization decreases range of motion, but does not improve collagen organization or tendon mechanical properties 12 weeks post-surgery⁷⁵. This further demonstrates the need for a period of protection for the healing insertion site. Surprisingly, complete removal of load, which differs from immobilization due to the absence of muscular tension, has been found to be detrimental to tendon healing⁷⁶. Therefore, a low, balanced and controlled load may be necessary to optimize rotator cuff insertion site healing and provide successful functional outcome following repair.

Surgical repair

Without optimal suture configuration, the injured tendon will not remain approximated to the bone insertion during healing, contributing to high failure rates in cuff repairs. The suture configuration must initially provide superior strength without impeding blood flow or damaging the tendon.

The sheep model has been used to study suture configuration based on the loads that the rotator cuff experiences. Tendon repairs were first studied in the sheep comparing bone tunnels and anchors. Differences were only found at time zero demonstrating that bone tunnels had higher failure loads⁷⁷. Further studies demonstrated the modified mason-allen suture technique is superior compared to other simple suture configurations, but both techniques caused similar tissue damage within the distal tendon¹⁵. Variations in the modified mason-allen did not demonstrate differences in mechanical properties^{78,79}, but did show increased expression of collagen II and improved fibrocartilage at the insertion site for the modified mason-allen⁸⁰. In a rabbit model, no clear differences in mechanical properties and histology were observed between single and double row repairs; however, the double row had less failures over the course of healing⁸¹.

One of the challenges of chronic rotator cuff repair is overcoming the large tension required to re-approximate the re-

tracted tendon back to the anatomic footprint. In a rat rotator cuff tear model, tension increased over time⁵⁵, suggesting the longer a cuff tear remains untreated the more difficult it is to repair. Further, as the tension to re-approximate the tendon to the anatomic footprint increased, the strength of the healing tendon decreased⁸². Similar results were also found clinically⁸³.

Augmentations

Rotator cuff augmentations have been studied using autografts, scaffolds or biologic additives such as growth factors. Autografts represent a more traditional approach to augmentation; however, sophisticated tissue engineering methods and designs allow for manipulation of various factors to improve the response. An ideal scaffold will promote fiber integration in the correct alignment, allow for cell integration, and will not initiate a negative biologic response.

A variety of autograft tissues have been used experimentally in rotator cuff repairs. A fascial autograft in a rabbit model was attempted due to its strength and ability to resist multidirectional loads. Based on histology, the fascial autograft remodeled the tendon insertion site with fibrocartilage by 8 weeks, demonstrated by the distribution of collagen types II and III⁸⁴. A patellar tendon-bone and a free flexor-tendon graft have also been examined in both a canine and sheep model. These studies demonstrated improved mechanical properties and histology grades in the patella tendon-bone grafts compared to the free flexor-tendon graft⁸⁵. The patella tendon-bone graft also had increased mechanical properties overtime¹⁶. Although autografts have not been used frequently, they may have potential for rotator cuff repair augmentation.

The dermal matrix graft is a biologic, acellular graft with its original structural collagen network intact. Dermal grafts were used as a patch to connect the injured tendon back to the anatomic footprint. Both a canine and sheep model was used to evaluate the ability of the dermal graft to augment rotator cuff repair and healing^{86,87}. The structural strength of the healing graft was decreased compared to controls at 6 weeks, however there were no group differences at 9 weeks. The graft was not fully integrated into the bone and there was an accumulation of macrophages at 9 weeks, which resolved by 24 weeks^{86,87}.

Periosteum contains multipotent stem cells that have the potential to differentiate into osteogenic and chondrogenic tissues. This tissue, tested in rabbits, was shown to improve the attachment strength. Histology showed that the cambium layer of periosteum could serve as a potent interface between tendon and bone and, with time, progressively mature and organize⁸⁸.

Another biologic scaffold tested in animal models is porcine small intestine submucosa (SIS), originally thought to be a cell-free, biocompatible biomaterial. However, porcine SIS caused noninfectious edema and severe pain in human patients who used the graft for tendon repair⁸⁹. When used in rabbits for rotator cuff repair, porcine SIS caused an inflammatory reaction characterized by massive lymphocyte infiltration. It was determined that SIS is not an acellular collagenous matrix and that it contains porcine DNA⁸⁹. In a sheep model, the SIS repair had greater stiffness between 12 and 24 weeks with patch reabsorption and the presence

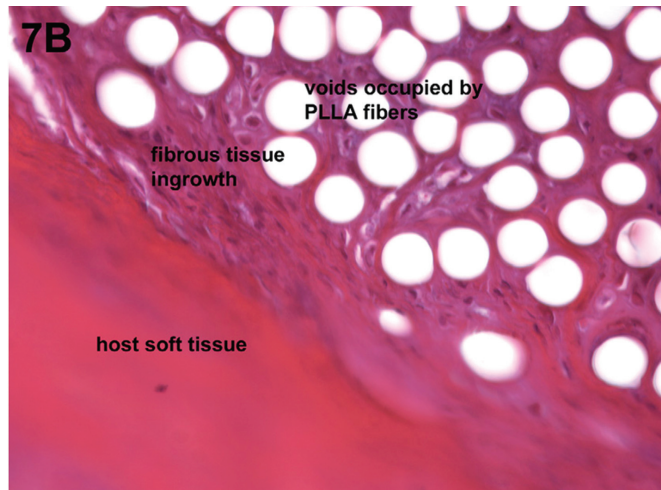


Figure 5. Host cell response to a poly-L-lactide scaffold demonstrating regions of fibrous tissue ingrowth, some of which appears fibrocartilagenous in a canine model. (Reprinted with kind permission of Rockwater Inc. (<http://rockwaterinc.com/>) from Derwin KA, Codsì MJ, Milks RA, Baker AR, McCarron JA, Iannotti JP. Rotator cuff repair augmentation in a canine model with use of a woven poly-L-lactide device. *J Bone Joint Surg Am* 2009;91-5:1159-71).

of diverse tissue types, including ectopic bone^{87,90}. The inflammatory complications found in rabbits and sheep did not manifest in rats or canines. SIS in rats resulted in improved biomechanical and histological properties compared to an unrepaired tendon⁹¹. A tendon-like structure similar to normal supraspinatus tendon tissue in the SIS group was observed⁹². Canine models have found that the failure strength of the graft was less compared to native tendon; however, failure strength was not different compared to the non-SIS repair. Histological findings were similar between groups with no signs of foreign body or immune-mediated reactions. Cross sectional area was found to increase overtime in the SIS group but not the non-SIS repair group⁹³. Based on animal research and clinical findings, SIS is not a viable tissue to use in rotator cuff repair augmentations. Structurally, there may be improvements over time in the mechanical properties; there is also inflammation associated with foreign body reactions.

Synthetic grafts have also been developed to provide initial repair strength and for the infiltration of cells to transform the graft into healthy tendinous tissue. Synthetic grafts can be made of several different biocompatible materials. Felt is one material that has been studied in animal models. In the canine model, several studies examined a variety of felt scaffolds to augment rotator cuff repairs. An increase in the mechanical properties of failure load and stiffness was observed during healing along with fibrous ingrowth in the tendon but not in the bone. At the tendon-to-bone insertion site, there were adverse side effects including foreign body reactions^{94,95}. A most recent study did not have biocompatibility issues but used a different form of felt, which also demonstrated successful fibrous tissue ingrowth (Figure 5)¹⁷.

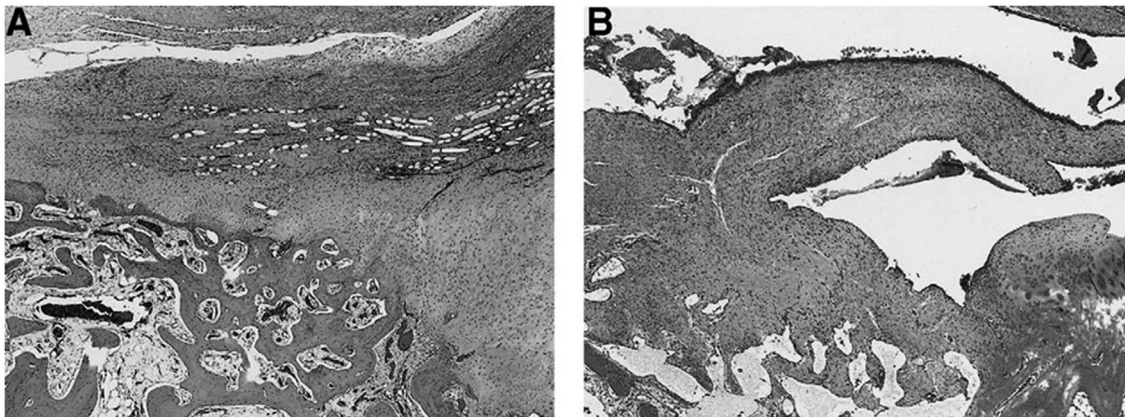


Figure 6. Sections stained with hematoxylin and eosin illustrating: a) well-aligned collagen fibers and trabecular bone ingrowths after repair with use of a chitin fabric scaffold and b) unaugmented control repair in a rabbit rotator cuff model. (Reprinted from Funakoshi T, Majima T, Suenaga N, Iwasaki N, Yamane S, Minami A. Rotator cuff regeneration using chitin fabric as an acellular matrix. *J Shoulder Elbow Surg* 2006;15:112-8, with permission from Elsevier).

Other synthetic scaffolds have also been examined for effectiveness in augmenting cuff repairs. Non-woven chitin fabric, an acellular matrix, was tested in rabbit infraspinatus tendons. Use of this fabric increased cellularity and improved collagen fiber alignment (Figure 6), resulting in regenerated tissues consisting of type III collagen along with improved structural properties⁹⁶.

Tissue engineered scaffolds have also been presented as possible materials to augment cuff repairs. One such material, a polyglycolic acid sheet, was used to repair a resected infraspinatus tendon in the rabbit model. The material allowed for the tendon insertion to be regenerated with a fibrocartilaginous layer consisting mainly of type III collagen; however, the material properties remained inferior to those of uninjured tendon⁹⁷. Due to the potential of adverse tissue reactions, the biologic response to an implant is commonly examined. A polycarbonate polyurethane patch was tested in rat supraspinatus tendon defects with no inflammatory reactions and excellent integration of tissue into the patch⁹⁸. Using an ovine chronic cuff repair model, a polyurethane scaffold mesh patch was tested and found to significantly improve the force at failure compared to nonaugmented controls, thus use of the material provides greater mechanical strength during healing than the traditional suture anchor repair alone⁹⁹.

The addition of cells or biologic additives to the rotator cuff is another approach to enhance repair. A chitosan-based hyaluron hybrid scaffold seeded with fibroblasts has been shown to increase production of type I collagen and the regenerated tissue in a large defect created in a rabbit infraspinatus. The fibroblast seeded scaffold significantly improved tensile strength and tangent modulus compared to a non-fibroblast seeded scaffold¹⁰⁰.

Tenocytes are another cell type being explored to improve massive rotator cuff tendon defects. Porcine small intestine submucosa and a type I/III collagen bioscaffold were used in

the rabbit to evaluate the impact of tenocyte addition in overcoming the inflammatory response induced by the scaffolds. Bioscaffolds seeded with tenocytes did display an inflammatory reaction, but to a lesser degree than the bioscaffolds alone, and produced a histological appearance more similar to control tendon. The addition of autologous tenocytes led to better tendon healing and remodeling than unseeded scaffold¹⁰¹.

Mesenchymal stem cells (MSCs) are a third type of cell applied in attempt to improve rotator cuff healing. Their effectiveness was tested in the rat by the application of MSCs in a fibrin carrier to the repair site at the time of surgery. No differences were determined in structure, composition, or strength of the healing tendon after MSC application, suggesting cell based strategies may require combination with growth and/or differentiation factors to be effective¹⁰². For example, adenoviral membrane type 1 matrix metalloproteinase (Ad-MT1-MMP)-transduced MSCs in a fibrin glue carrier was added to the repair site, which attempted to evade scar tissue formations at the repair interface and drive a regenerative process. Although no differences were detected between Ad-MT1-MMP transduced MSCs and unadulterated MSCs at 2 weeks, the Ad-MT1-MMP MSC treated group generated more fibrocartilage, higher ultimate load to failure, ultimate stress to failure, and stiffness values. This encourages the exploration of biologic augmentation to improve regeneration of the tendon-to-bone interface¹⁰³.

However, future studies are required to optimize which growth factors are most advantageous for tendon-to-bone regeneration after repair. For example, modulating MMP activity results in distinct changes in histologic observations and is one potential avenue for altering tendon-to-bone healing¹⁰⁴. Meanwhile, MSCs transduced with adenoviral-mediated gene transfer of human BMP-13 applied at time of surgical repair in the rat model did not result in improved properties¹⁰⁵.

The application of FGF-2 in conjunction with a dermal matrix

graft improved ultimate failure loads and histology scores with time¹⁰⁶. Ultimate failure loads were also comparable to controls, providing evidence for the use of FGF-2 during cuff repair. Another approach coated sutures with PDGF-bb found no differences in ultimate failure load, but improved histology scores¹⁰⁷.

In addition to enhancing tendon healing, attempts have been made to enhance bone healing. A variety of bone growth factors (osteoinductive bone protein extract, rhBMP-12 paste, and marrow supplementation, cartilage derived BMP-2) were used to enhance insertion site healing. An enhanced fibrocartilage zone, higher ultimate failure loads, and higher stiffness were observed¹⁰⁸⁻¹¹⁰. This approach demonstrates the feasibility to enhance cuff repairs with the implementation of both tendon and bone growth factors.

It is common for nonsteroidal anti-inflammatory drugs (NSAIDs) to be prescribed after surgical repair of the rotator cuff. The effect of celecoxib, a cyclooxygenase-2-specific NSAID, and indomethacin, a nonselective NSAID were evaluated. Both of these drugs resulted in worsened repair conditions, including complete failure to heal, lower failure loads, and poor collagen organization and maturation providing concern about administration of NSAIDs clinically¹¹¹.

Controversy also surrounds the use of anabolic steroids for cuff repair. The effect of nandrolone decanoate was examined in a surgical repair in a rat model which resulted in poorer healing and weaker tendon strength. It also led to focal fibroblastic reaction and inflammation compared to the extensive fibroblastic activity observed in groups without steroids¹¹².

Another approach for cuff repairs is through the use of bipolar radiofrequency energy, which is used to trigger healing through controlled inflammatory and angiogenic responses by disrupting the molecular bonds of collagen. However, this treatment had no definitive effect in improving acute supraspinatus repairs in the rat model¹¹³.

Systemic risk factors

Systemic factors can also have an effect on tendon degeneration and healing. In a rat cuff repair model, diabetes caused a decrease in ultimate failure load, stiffness, fibrocartilage and organized collagen at the tendon insertion site. There was also an increased deposition of advanced glycation end-products (AGE)¹¹⁴, produced by a chemical reaction between collagen and hyperglycemia¹¹⁵. AGEs are thought to be one of the culprits of diabetic related heart and renal disease^{116,117}.

Nicotine has been found to have a time dependent affect on tendon mechanical properties. Specifically, maximum stress decreased at early time points; however, maximum stress and modulus significantly increased at later time points^{118,119}. When examining the biological response, nicotine use resulted in lower cell proliferation, lower type I collagen expression at early time points, and higher inflammation at later time points¹¹⁹. Although the mechanisms by which diabetes and nicotine cause decreased rotator cuff healing are not known, the deleterious mechanical and biological effects are clear.

Translational applications

The goal of animal model research is to systematically test emerging theories and treatments in a controlled and consistent environment with the intention of improving patient care. As a consequence of animal studies related to the rotator cuff, several advances in clinical medicine have been made and a few examples are provided here. Animal models have been used to identify that overuse activity can cause rotator cuff tendon degeneration and rest is an effective treatment to restore normal tendon properties^{70,120}. The successful repair of chronically torn rotator cuff tears has been shown to be dependent on the amount of force required to reapproximate the tendon to the rotator cuff footprint⁸², and that the reapproximation force also increases with time⁵⁵. This information has led to, and supported, the timely repair of rotator cuff tears, decreasing the likelihood of a failed repair. Although the outcomes of many animal studies have yet to be clinically implemented, it is clear that an avenue exists for them to influence future clinical treatments. Work done on joint immobilization and remobilization has the potential to influence post-operative treatment and rehabilitation protocols. Similarly, experimentation in the clinic is avoided by the rigorous evaluation provided by animal research on treatments involving synthetic scaffolds and biologic additives. This improves the introduction of new treatments to the clinic.

Conclusion

In conclusion, animal models have been instrumental in identifying mechanisms of rotator cuff injury, evaluating rehabilitation, and assessing surgical alternatives. Unlike clinical research, animal model research has the ability to conduct well controlled experiments on a consistent population, with the capacity to run a large number of assays, and without the interference of confounding factors. The ability to experiment with new synthetic devices, scaffolds, and growth factors to examine the biologic response prior to implementation in patients further enhances the appeal of animal models. Although animal models can be used to address many clinically relevant questions, they can never replace the human in research; however, it does provide a starting point to investigate novel ideas and theories.

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