SHOULDER

Biocompatibility of a polymer patch for rotator cuff repair

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Abstract Both mechanical and biological factors
influence the high re-tear rate after rotator cuff repair.
Mechanical factors have largely been addressed by the
introduction of better implants and modification of
suture configuration, but further improvements are
needed to address the often poor tissue quality of the
degenerated rotator cuff tendons. Current biological
solutions provide only short-term reinforcement and
have been associated with pseudo-infectious reactions.
This pre-clinical animal study investigates the biologi-
cal response to a novel polycarbonate polyurethane
patch used for tissue augmentation in a rat rotator cuff
repair model. Bilateral defects were created in the
supraspinatus tendons of 12 Sprague Dawley rats. One
side was repaired with a patch as a tissue augmentation
device. The contralateral side acted as internal control
without patch augmentation. After 6 weeks the tissues
were harvested and underwent histologic and histo-
morphometric analyses. Histological evaluation dem-
onstrated no inflammatory reaction; histomorphometry
revealed tissue ingrowth of 79.9%. In conclusion, the
polycarbonate polyurethane patch for tissue extension
or augmentation in rotator cuff repair has demon-
strated no inflammatory response and excellent tissue
integration in a rat rotator cuff repair model.

Keywords Rotator cuff · Animal model ·
Biocompatible material

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Introduction

Presently, good to excellent clinical results are found in
a high percentage of cases with follow-up as long as
10 years after rotator cuff repair [1, 2], even though
other studies have demonstrated structural failure of
the repair in 20–90% of cases [3–6]. The reasons for
this discrepancy are controversial, but a consensus
exists that intact repairs provide better results than
failed ones [5]. In an attempt to decrease structural
failure rates, technological improvements have been
made to address repair failures due to anchor pull-out
or suture fatigue. However, the issue of suture pull-out
from weakened or compromised rotator cuff tendon
tissue remains to be solved.

In order to reduce re-tear rates secondary to suture
pull-out, several groups have investigated techniques
to augment the weakened rotator cuff tissue, such as
porcine small intestinal submucosa (SIS). These bio-
logical allo- or xenografts carry the risk of disease
transmission or sub-clinical immune response, espe-
cially since recent reports have demonstrated the per-
sistence of porcine donor cells in SIS grafts [7]; some
reports have shown significant inflammatory responses

with massive leukocyte infiltration [7]; and lastly, biological grafts lose integrity over time as demonstrated by a greater than 90% re-tear rate of massive rotator cuff tears reinforced with the porcine SIS patch [8].

Most rotator cuff tears are degenerative in nature and result from extrinsic factors, such as mechanical compression, and intrinsic factors, such as the zone of relative hypovascularity just proximal to the insertion. While extrinsic factors can be addressed at the time of reconstruction through decompression, intrinsic factors currently have no specific treatment. Without augmentation, the same weakened tissue that had degenerated to a point of spontaneous failure cannot be expected to heal and provide lasting stability following repair. Biological implants provide only short-term reinforcement without tissue regeneration. Therefore, a non-resorbable implant, similar to those used for vascular reconstructions or hernia repairs provides an appealing approach [9]. These implants have an excellent clinical record and offer a permanent benefit to construct stability [10].

Due to large stresses and repeated motion, the shoulder poses specific challenges to a synthetic material that is expected to provide long-term stability. The polymer polycarbonate polyurethane has mechanical and biologic properties that make it suitable for use as an implantable device to augment soft tissue repair. Unlike the polyesters polyurethane and polyether polyurethane, which are subject to hydrolytic and oxidative degradation [11], polycarbonate polyurethane has superior biostability while possessing appropriate resistance to various mechanical loadings and demonstrating resilient recovery. Specifically, ChronoFlex AL55D is a polycarbonate polyurethane that has demonstrated no hydrolytic degradation in long-term in vivo tests [12]. Stokes et al. simulated environmental stresses in vivo by using excessive strain as the accelerant followed by implantation into the subcutaneous tissue in rabbits for 12 weeks [13]. The material exhibited no evidence of environmental stress cracking, suggesting that this material may be a suitable augmentation device in applications such as rotator cuff repair that experience significant fatigue due to constant motion, tension, and shear stress.

To be suitable for implantation, a material has to not only have mechanical advantages and have features that allow it to be used as a scaffold for tissue ingrowth and regeneration, but also be biocompatible ideally demonstrated in an experimental model designed to resemble the clinical scenario as closely as possible. A prior study evaluating a polytetrafluoroethylene graft has raised concerns regarding possible foreign body and inflammatory reactions [14].

The aim of this study therefore was the evaluation of this new patch material in a rat rotator cuff repair model, focusing on the evaluation of potential inflammatory changes in response to implantation of the polycarbonate polyurethane polymer. Our hypothesis was that the material would provide a biocompatible matrix facilitating tissue ingrowth and supporting a stable repair site.

Materials and methods

Patch material

The patch material is a porous matrix made from cross-linked elastomeric polyurethane foams based on polycarbonate polyol and aromatic isocyanate (Biomerix Corporation, Somerset, NJ, USA). The porous matrix is designed as an open structure that is characterized by interconnected and intercommunicating pores (Fig. 1). The material is elastomeric and demonstrates resilient recovery after being deformed under both compression and tension (Table 1). Further, it is biostable owing to its chemical structure that resists hydrolytic and enzymatic biodegradation. For surgical implantation, the matrix is sized and shaped appropriately from a block of the polyurethane foam and sterilized by gamma radiation.

Experimental setup and animal care

After approval of the experimental protocol by our Institutional Animal Care and Use Committee, six male Sprague Dawley rats (250–275 g) underwent rotator cuff repair. All animals were housed in ap-
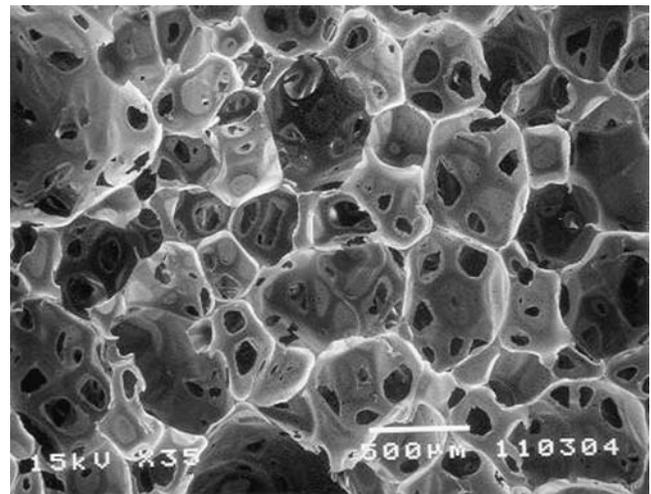

Fig. 1 Scanning electron microscopy image of the patch material (bar equals 50 μm)

Table 1 Material properties of the patch material

Density	48.1 kg/m^3
Average cell size	275–350 μm
Tensile strength	170–275 kPa
Elongation at failure	150% at 50% strain
Compressive strength	7–14 kPa
Compression set	4–8%
Dynamic resilient recovery time	<15 s (75% compression for 10 min)
Intrusion volume accessible to fluids	25–30 cm^3/g
Darcy's liquid permeability	150

proved facilities, and were allowed to move freely in their cages while being monitored daily for post-surgical complications. In general, animal care adhered to the standards defined in ''Principles of laboratory animal care'' (NIH publication No. 86-23, revised 1985). Pain management was achieved by subcutaneous injection of Buprenorphine 0.01–0.03 mg/kg pre-operatively, and every 10–12 h thereafter as needed for demonstrated pain. There were no surgical site infections or other complications.

Operative procedures

All animals were anesthetized with an intramuscular injection of Ketamine (100 mg/kg) and Xylazine (5 mg/kg). Antibiotic prophylaxis was provided by subcutaneous injection of Cefazolin (22 mg/kg) 30 min before surgery, and then daily for a total of 7 days. Subsequently, the upper extremities were shaved, aseptically prepped and draped.

The surgical exposure involved 2 cm incisions over the dorsal aspects of the shoulder and scapula bilaterally. In each shoulder, the scapular spine was identified, and the deltoid muscle was split in line with its fibers over a distance of 1 cm. The subacromial bursa was opened but not excised. The supraspinatus tendon was visualized as it passed underneath the coracoacromial arch to its insertion on the greater tuberosity of the proximal humerus.

Bilateral full thickness defects were created 1 mm proximal to the supraspinatus tendon insertion with a no. 15 scalpel blade without removal of tendon substance. The defects in both sides were then repaired to the insertion site on the greater tuberosity with two 5-0 Prolene (Ethicon Inc., Somerville, NJ, USA) sutures through transosseous tunnels. On the control side, no further reinforcement was performed. On the experimental side, the repair was additionally reinforced by oversewing with a polycarbonate polyurethane patch, creating a layered construct consisting of patch and tendon.

The deltoid muscle was then re-approximated in both shoulders with interrupted 4-0 Vicryl (Ethicon) suture, and the skin was closed with 3-0 Monocryl (Ethicon).

Sacrifice and specimen procurement

All animals were sacrificed 6 weeks post-operatively by carbon dioxide inhalation. Both shoulders were evaluated macroscopically for gross evidence of healing, suture encapsulation, loose bodies and inflammatory reactions. Subsequently, the supraspinatus tendon and proximal humerus were removed and fixed in 10% neutral buffered formalin.

Analyses

Histology

The specimens were decalcified before being embedded in paraffin for histological processing. Slides were stained with hematoxylin and eosin (H&E) for routine histologic assessment for reactive changes such as the presence of inflammatory cells and inappropriate vascularization. Sections were also stained for collagen and polarization microscopy according to the following protocol: slides containing sections were placed in xylene at 37°C for 12 h to remove the strongly birefringent paraffin, hydrated in a series of ethanol of decreasing concentration (between 100 and 50%) and then finally placed in water. Prior to staining with the Picrosirius red solution, dewaxed and hydrated sections were treated at 37°C for 18 h in 2 mg bovine testicular hyaluronidase in 1 ml of 0.1 M phosphate buffer at pH 6.0 to remove chondroitin sulfate molecules, which can mask the cationic binding sites of the collagen for polyanionic Sirius red molecules. Sections were then stained for 30 min in a solution of 0.1% Sirius red F3B (Polysciences, Warrington, PA, USA) dissolved in saturated picric acid. Sections were dehydrated in absolute ethanol for 9 min (three changes for 3 min each), cleared in a 1:1 mixture of absolute ethanol and xylene for 3 min, and in xylene for 9 min (3 changes for 3 min each) before cover slips were mounted. Stained sections were analyzed with a Nikon polarization microscope equipped with a $\lambda/4$ compensator plate and interference filter ($\lambda = 589$ nm). All histology was independently reviewed by two blinded investigators.

Histomorphometry

To quantify soft tissue ingrowth into the patch, microscopic images were digitized for histomorpho-

metric analysis utilizing the Metamorph Imaging System (Series 6.1, Universal Imaging Corp., West Chester, PA, USA). The patch cross-sectional area was selected as the region of interest (ROI), and the reparative tissue within this ROI was marked by manual thresholding. The software then calculated the relative area ratio of reparative tissue compared to the total patch size. This process was repeated in three different and representative sections for each specimen. The resultant area ratios were then averaged for each group.

Results

Gross inspection at the time of retrieval revealed a yellowish appearance of the patch with good integration into the tendon and bone, and no gross inflammatory changes. The control shoulders demonstrated unorganized scar tissue at the defect site. All rotator cuff repairs were structurally intact. Both sides showed minimal scar tissue and adhesions in the subacromial space and subdeltoid region, consistent with post-surgical changes.

On routine histological exam, neither experimental nor control shoulders demonstrated inflammatory cells or inappropriate vascularization 6 weeks after surgery. In control specimens, routine histology and polarized microscopy confirmed the gross observation of unorganized scar tissue filling the defect (Fig. 2). In patch repair specimens, however, the collagen fibers were aligned within any given pore compartment of the patch. The organization was that of regular connective tissue with dense collagen fibers. It was also noted that
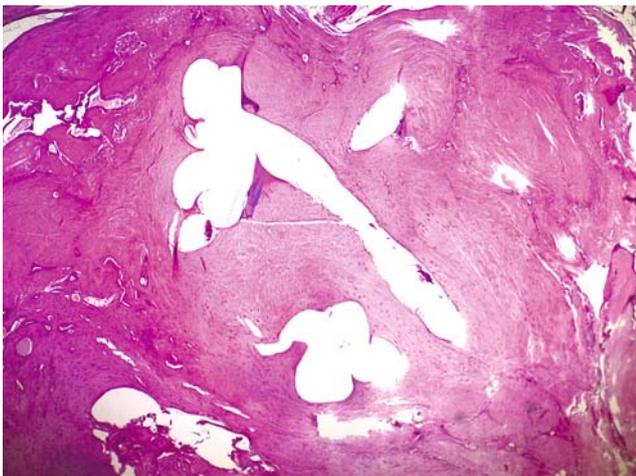
the reparative tissue infiltrating the patch was well integrated with the tendon of the supraspinatus (Fig. 3) and the tendon attaching to the humerus (Fig. 4). Cells growing closer to the walls of patch material were noted to have larger and rounder nuclei, consistent with active matrix production. The cells further removed from the walls had flatter, lighter staining nuclei, consistent with more quiescent cells.

Histomorphometric analysis demonstrated an average patch infiltration with connective tissue of 79.9% (SD ± 7.69%).
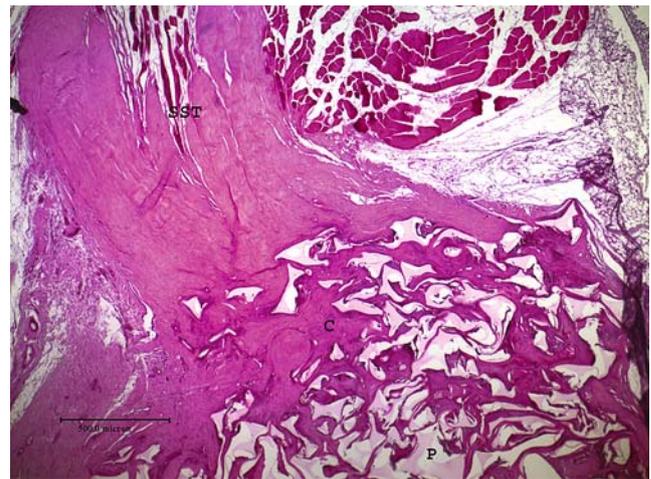

Fig. 3 Histologic image of a patch repair depicting the supraspinatus musculotendinous junction (*SST*). Collagen fibers (*C*, *dark pink*) are shown infiltrating the patch material (*P*, *light pink*) (H&E stain, ×40 magnification)

Fig. 2 Histologic image of a non-repaired control side demonstrating lack of global organization of the collagen bundles (H&E stain, ×40 magnification)
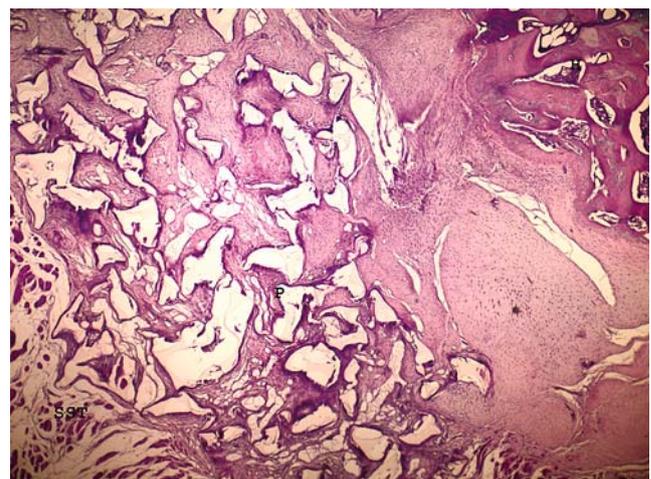

Fig. 4 Histologic section of a patch repair depicting the rotator cuff footprint: supraspinatus tendon (*SST*), patch material filled with connective tissue (*P*), humeral cortex (*H*) (H&E stain, ×40 magnification)

Discussion

This study investigated the biocompatibility of a new polymer patch material for the augmentation of soft tissue repairs, such as in rotator cuff tears. Because failure of rotator cuff repair generally occurs at the tendon-suture interface with failure to effectively heal to the greater tuberosity, we strongly believe that a non-absorbable solution to permanently strengthen the reconstruction will lead to reduced re-tear rates following rotator cuff repair.

Histological examination revealed no inflammatory changes and good patch integration, as demonstrated by near complete filling of the porous patch by reparative tissue. The specific experimental model used for this study is well established in the literature [15–18]. The anatomy of the rat shoulder closely approximates the human shoulder, and the procedure is similar to that used in clinical practice. Therefore, the experimental model used is relevant to the clinical problem this study investigates.

In normal supraspinatus tendon tissue, collagen bundles are oriented in a parallel fashion along the longitudinal axis of the tendon. For the patch repair group, connective tissue was uniformly oriented within each patch pore but did not demonstrate global orientation with respect to the longitudinal axis of the tendon. This likely represents a continuous and parallel bundle of collagen weaving between the patch struts, thus moving in and out of the plane of section. Histomorphometry revealed tissue ingrowth of almost 80%, suggesting that the open-pored structure of the patch material is conducive to tissue ingrowth. Also, there was no hypertrophic scar tissue in the vicinity of the patch material.

This project has several limitations, since it was primarily designed to assess potential inflammatory responses and tissue ingrowth into the patch material. Intuitively, the patch will confer improved strength to the repair. However, no biomechanical testing was conducted at this stage to confirm this hypothesis, but will be performed in future studies. Furthermore, the patch was tested in healthy tissue in a rodent model that does not necessarily reflect the degenerative nature of rotator cuff tears seen in clinical practice. We cannot extrapolate whether degenerated tissue would mount a similar reparative response with tissue ingrowth into the patch. However, since the patch is non-resorbable, it confers permanent stability to the construct, irrespective of tissue ingrowth.

In conclusion, the data demonstrated findings consistent with good biocompatibility within the confines of our model. In particular, there was good filling of the patch material with organized collagenous tissue, absence of hypertrophic scar tissue surrounding the patch, and no inflammatory changes either on gross examination or histology. Further studies in a larger animal model will evaluate the biomechanical properties of the tendon-patch construct.

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