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SURGICAL ENDOSCOPY
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# Histologic results 1 year after bioprosthetic repair of paraesophageal hernia in a canine model

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**Abstract**
*Background:* The use of prosthetic materials for the repair of paraesophageal hiatal hernia (PEH) may lead to esophageal stricture and perforation. High recurrence rates after primary repair have led surgeons to explore other options, including various bioprostheses. However, the long-term effects of these newer materials when placed at the esophageal hiatus are unknown. This study assessed the anatomic and histologic characteristics 1 year after PEH repair using a U-shaped configuration of commercially available small intestinal submucosa (SIS) mesh in a canine model.
*Methods:* Six dogs underwent laparoscopic PEH repair with SIS mesh 4 weeks after thoracoscopic creation of PEH. When the six dogs were sacrificed 12 months later, endoscopy and barium x-ray were performed, and biopsies of the esophagus and crura were obtained.
*Results:* The mean weight of the dogs 1 year after surgery was identical to their entry weight. No dog had gross dysphagia, evidence of esophageal stricture, or reherniation. At sacrifice, the biomaterial was not identifiable grossly. Biopsies of the hiatal region showed fibrosis as well as muscle fiber proliferation and regeneration. No dog had erosion of the mesh into the esophagus.
*Conclusions:* This reproducible canine model of PEH formation and repair did not result in erosion of SIS mesh into the esophagus or in stricture formation. Native muscle ingrowth was noted 1 year after placement of the biomaterial. According to the findings, SIS may provide a scaffold for ingrowth of crural muscle and a durable repair of PEH over the long term.

**Key words:** Laparoscopy — Paraesophageal hernia — Small intestinal submucosa

Studies have shown that surgical repair of paraesophageal hernias (PEH) is associated with a high recurrence rate [1–5]. It has been hypothesized that for large hernias, reinforcement of the hiatal closure with mesh may reduce recurrence rates. Tension-free hernia closure with synthetic mesh has been reported [6–11]. However, repair with synthetic mesh may occasionally result in stricture, perforation, or erosion of the mesh into the esophagus [12].

The use of a bioscaffold such as small intestinal submucosa (SIS) mesh (Cook Biotech Inc., West Lafayette, IN) for PEH surgery also has been reported [13]. However, the long-term effects of this acellular material at the esophageal hiatus are unknown. This study assessed the anatomic and histologic characteristics after PEH repair with SIS mesh in a canine model to further understanding concerning the natural history of this bioprosthetic material around the esophageal hiatus.

## Methods and materials

### *Animals*

Animal Research Committee approval for all the surgical procedures and other experiments at the Washington University School of Medicine and the Barnes-Jewish Hospital was obtained. The study animals were maintained in accordance with the guidelines prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council.

Six mongrel dogs weighing 40 to 50 lb were used. All six animals underwent thoracoscopic creation of a hiatal hernia (Table 1), followed by laparoscopic repair of the PEH with a four-ply section of SIS mesh. The mesh was cut into a U shape rather than a key-hole configuration to lessen the likelihood of postoperative stricture [14] (Table 2).

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**Table 1.** Thoracoscopic creation of paraesophageal hiatal hernia (PEH)

- Left-sided thoracoscopic approach
- Phrenoesophageal membrane dissected and divided at the gastroesophageal junction
- Lower esophagus and gastric fundus retracted into the posterior mediastinum
- Gastric body secured to the left crus of the diaphragm with nonabsorbable sutures
- Red rubber catheter inserted for evacuation of the pneumothorax
- Upper gastrointestinal (UGI) series and endoscopy performed to document PEH 2 weeks postoperatively

**Table 2.** Laparoscopic paraesophageal hiatal hernia (PEH) repair

- PEH repair 30 days after hernia creation
- Five-port technique: 10-mm port (liver retractor); remainder 5 mm
- Hernia contents reduced into the abdomen
- Crural ring dissected circumferentially from the esophagus
- Small intestinal submucosa (SIS) mesh secured using multiple interrupted nonabsorbable sutures without primary closure of the crura
- Soft diet maintained postoperatively for the life of the animal
- Animals killed 12 months after hernia repair
- Upper gastrointestinal (UGI) series and endoscopy performed before animals are killed
- Multiple biopsies of the periesophageal tissue obtained

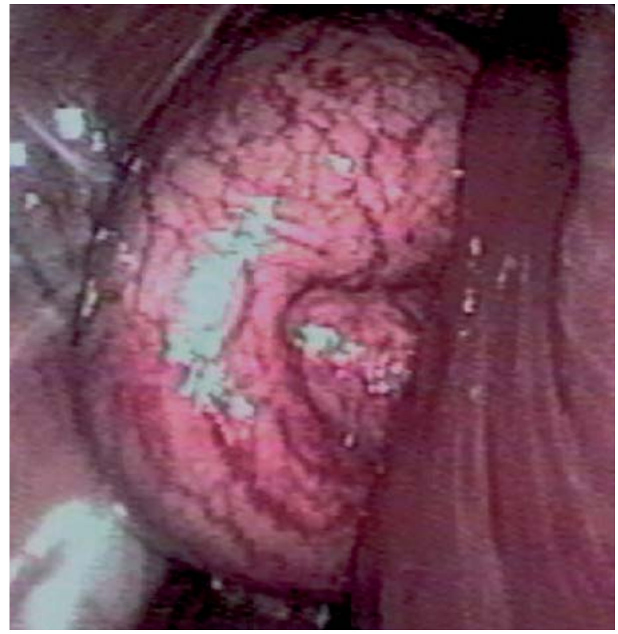

**Fig. 1.** Appearance of the fundus above the diaphragm after thoracoscopic paraesophageal hernia creation via the left chest.

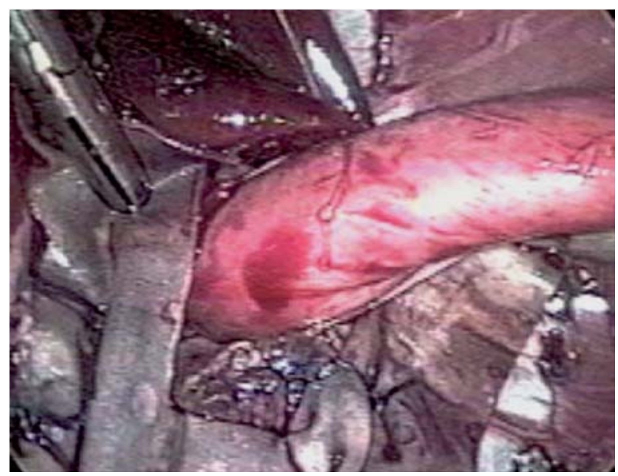

**Fig. 2.** Placement of a U-shaped configuration of small intestinal submucosa (SIS) mesh over the crural opening without primary closure of the crura.

## *Operative techniques*

After an overnight fast, the animals were premedicated with Telazol/xylazine/ketamine. Anesthesia was maintained with isoflurane. Local anesthesia with bupivacaine 0.5% was used at all port sites. After insertion of an endotracheal tube and its connection to a ventilator, tidal volumes of 15 to 20 ml/kg at a rate of 20 breaths/min with peak inspiratory pressure of 15 to 25 cm $H_2O$ were maintained, and continuous end-tidal $CO_2$ monitoring was performed. Postoperative analgesia was given on an as-needed basis.

The hiatal hernia was created via a left-sided thoracoscopic approach using three ports. The inferior pulmonary ligament was initially divided. After identification of the esophagus and vagus nerve, the phrenoesophageal membrane was divided, and the gastroesophageal junction was circumferentially dissected. The lower esophagus and the gastric fundus were retracted into the posterior mediastinum. The gastric body was secured to the posterior left crus of the diaphragm with three nonabsorbable sutures (Fig. 1).

At completion of the procedure, a red rubber catheter was inserted into one of the port sites for evacuation of the pneumothorax. The port sites were closed using interrupted absorbable sutures. A Heimlich valve was applied to the distal end of the red rubber catheter as anesthesia was discontinued and the dog was weaned from ventilatory support. After the dog's removal from ventilatory support, the Heimlich valve was removed, and the red rubber catheter was aspirated with a 60-ml syringe to ensure complete evacuation of the pneumothorax. The red rubber catheter was removed, and the site was closed.

The animals were given liquids the night of surgery, then placed on a regular diet on postoperative day 1. The animals were observed for 1 additional day, then returned to routine housing.

A laparoscopic PEH repair was performed 4 weeks after creation of the hernia. The animal was placed in the supine position. After abdominal insufflation and insertion of five laparoscopic ports, the left lateral segment of the liver was elevated with a fan retractor, and the stomach and epiphrenic fat pad were retracted inferiorly. The intrathoracic contents of the hiatal hernia were reduced using atraumatic graspers and a careful hand-over-hand technique. To gain the appropriate plane for dissecting the hernia out of the mediastinum, the tissues that form the border between the hernia contents and the crural margin were divided. Blunt dissection then was continued up into the mediastinum while the hernia contents were swept back toward the abdominal cavity. This combination of sharp and blunt dissection was continued until the entire anterior circumference of the crural arch was freed from the hernia sac. Long blunt motions were used to sweep the sac inferiorly, exposing the right lateral border of the esophagus and posterior vagus nerve, as well as the anterior and left side of the esophagus and anterior vagus nerve. In these animals, the tissues did not readily separate. There usually were adhesions of variable density between the sac and the pleura and other mediastinal structures, which were divided with ultrasonic shears.

After circumferential dissection of the esophagus and exposure of the right and left crura junction, the dimensions of the defect were measured. A patch of four-ply SIS was fashioned into a U shape according to dimensions of the hernia defect without closure of the crura primarily. The width of the defect was generally 4 to 5 cm.

After insertion of the mesh into the abdominal cavity, the patch was unrolled near the hiatus, and one limb was passed posterior to the esophagus. The patch widely overlapped the posterior margin of the crura and laterally for several centimeters on each side. The patch was sewn with interrupted 2-0 polyester sutures to the edges of the defect

**Fig. 3.** Upper gastrointestinal series 2 weeks after hernia creation showing the upper stomach above the diaphragm.

(Fig. 2). At completion of the case, the port sites were closed in two layers with absorbable interrupted sutures.

Postoperatively, the animals were allowed liquids overnight, then advanced to a soft diet in the morning. A soft, canned food diet then was maintained for the life of the animal. The animals were observed for 10 days, then returned to routine housing. The animals were killed 52 weeks after the hernia repair.

### *Upper gastrointestinal series*

An upper gastrointestinal series was performed 2 weeks after hernia creation and immediately before the animals were sacrificed to determine the presence or absence of a hiatal hernia (Fig. 3). After light sedation with xylazine, the animal was administered oral barium contrast, and the examination was completed with the animal under fluoroscopy.

### *Esophagogastroduodenoscopy*

Esophagogastroduodenoscopy was performed 2 weeks after hernia creation and before the animal was sacrificed while under general anesthesia. An adult gastroscope was used to determine the presence or absence of a hiatal hernia and to document any mucosal changes in the esophagus or stomach.

### *Histology*

When the animals were killed, multiple biopsies of the esophagus and paraesophageal tissue were obtained for histologic evaluation. In particular, specimens posterior to the esophagus at the site of mesh placement were obtained. Specimens were fixed in 10% neutral buffered formalin, imbedded in paraffin, and sectioned at 5 $\mu$m. Slides were stained with hematoxylin and eosin (H&E) or Masson's trichrome.

## Results

At the 1-year follow-up assessment, the mean weight of the dogs (53.8 lbs) had increased slightly, as compared with their entry weight (49.7 lbs, nonsignificant difference). No dogs showed gross dysphagia, evidence of esophageal stricture, or reherniation on upper gastrointestinal series before they were killed. Esophagogastroduodenoscopy showed no evidence of stricture or hiatal hernia, and normal mucosa was present in the esophagus and stomach of all the animals. There was no evidence of esophageal or gastric mucosal inflammation, erosion, or ulcer.

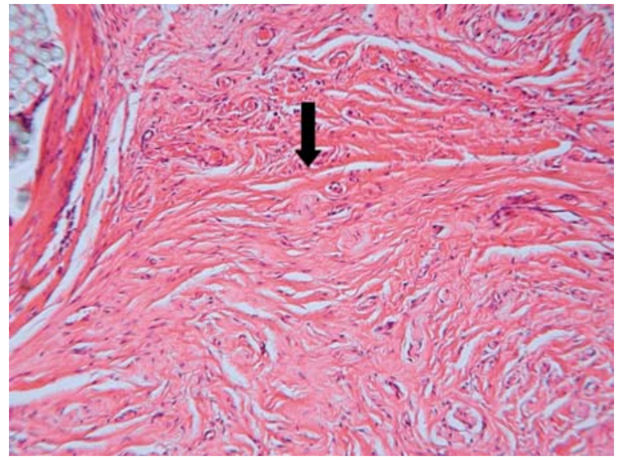

**Fig. 4.** Hematoxylin and eosin (H&E) stain of the fibrovascular scar with muscle fibers staining more eosinophilically (*black arrow*).

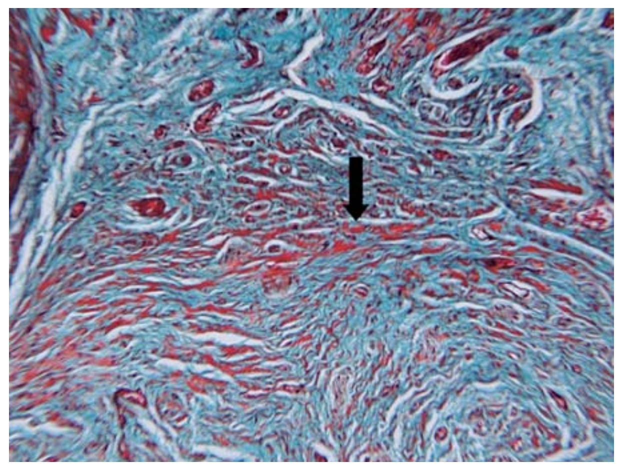

**Fig. 5.** Trichrome stain of a fibrovascular scar showing infiltration of proliferating muscle fibers (*staining red*).

When the animals were sacrificed, the SIS biomaterial was not identifiable grossly. The histology of all six dogs was similar. Regenerating muscle cells were characterized by slightly vesicular, centrally located nuclei and lightly basophilic cytoplasm on H&E stain. The biomaterial was not identifiable, but had been replaced with mature fibrovascular scar tissue (Figs. 4 and 5). There was active fibrosis around most sutures, characterized by numerous fibroblasts surrounding and infiltrating the area (Fig. 6).

On trichrome stains, cytoplasm stained red as expected for muscle. Within the fibrotic area, there was evidence of significant muscle fiber proliferation. Muscle bundles showed irregular or partial organization. The

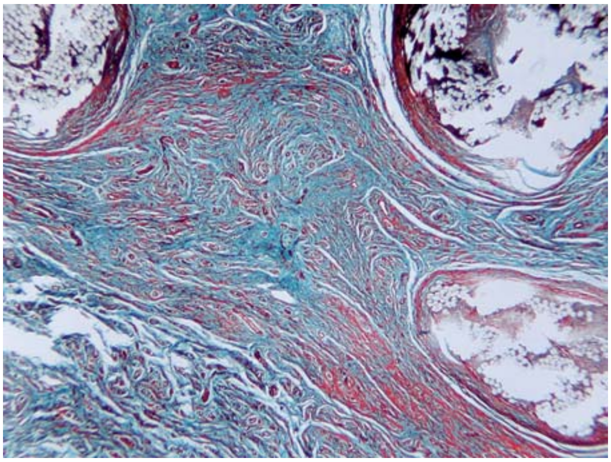

**Fig. 6.** Trichrome stain showing active fibrosis characterized by numerous fibroblasts surrounding the sutures.

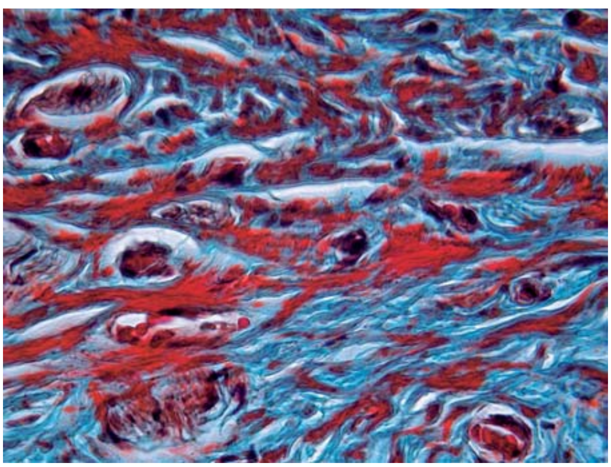

**Fig. 7.** Trichrome stain showing proliferation of muscle fibers (*red*) within the fibrovascular scar (magnification ×400).

muscle regeneration was characterized by small bundles of cells and individual cells irregularly arranged within the scar tissue (Fig. 7). Proliferation was more intense near the border with normal skeletal muscle. Approximately 30% to 50% of the surgical site was regenerating muscle. Ingrowth of the mesh or its replacement tissue into the esophagus was not seen in any dog.

## Discussion

When large hiatal hernias are repaired with simple primary crural closure, the anatomic failure rate may exceed 40% [4]. For the past decade, U.S. surgeons have increasingly used prosthetic patches to repair abdominal wall and groin hernias [15, 16]. Current wisdom suggests that eliminating tension on the repair while using materials of supraphysiologic strength lessens the postoperative recurrence rate [16]. Using the same rationale, it has been hypothesized that the use of mesh may decrease the rate of reherniation after repair of large hiatal hernias.

The concern about anatomic recurrence after laparoscopic PEH repair has led some surgeons to selective use of prosthetic mesh reinforcement in repairing large hiatal defects [17, 18]. In addition, a prospective, randomized trial comparing laparoscopic polytetrafluoroethylene (PTFE) patch repair and simple cruroplasty for large hiatal hernias concluded that the use of prosthetic cruroplasty reinforcement for large hiatal hernias may prevent hernia recurrences [19].

Despite these data, surgeons have been reluctant to use mesh or other prosthetic material at the gastroesophageal junction because of concern for erosion of the foreign material into the esophagus and its migration into surrounding tissue [12]. There are few published reports of this dreaded complication, but many "expert" surgeons have recounted anecdotes of patients with complications of prosthetic material at the esophageal hiatus associated with both polypropylene and PTFE patches (unpublished observations).

Recently, it has been suggested that reinforcement of the hiatal closure with SIS mesh might reduce recurrence rates without causing injury to the esophagus [13]. The extracellular matrix derived from porcine SIS has been used as a scaffold for body wall repair in a number of preclinical animal studies [20–24]. The findings have shown replacement of the matrix by skeletal muscle in small and large animal studies [25]. However, the long-term effects and the host tissue response to this xenogeneic material at the esophageal hiatus are unclear.

The current study helps to clarify the long-term effects of SIS placed at the esophageal hiatus in an animal model. None of the six dogs had evidence of PEH recurrence 1 year after repair of an iatrogenic PEH, which suggests that SIS (4 ply) may provide a durable repair. At gross inspection, the SIS extracellular matrix was unrecognizable and replaced by what appeared to be host-derived tissue. Histologically, host tissue, which included fibrous connective tissue and skeletal muscle, replaced the SIS. In a number of histologic samples, muscle proliferation was interspersed within the fibrovascular scar. These results suggest that the muscle fibers were not sampled from the surrounding diaphragm. Furthermore, although scarring occurred around the esophageal hiatus, there was no evidence of ingrowth of the surrounding tissue into the esophagus or stomach.

This long-term study of PEH repair in a canine model suggests that an acellular biomaterial such as SIS not only may function as a buttress for hiatal hernia repair, but also may provide a scaffold for native ingrowth of connective tissue and skeletal muscle. To our knowledge, this is the first long-term observational study investigating the fate of SIS mesh placed at the esophageal hiatus. Given that this experience was with dogs rather than humans, and that the total number of experimental subjects was small, these excellent results may not necessarily be extrapolated to the clinical arena. However, these initial observations support the concept that a bioprosthetic (SIS) mesh patch may be a safe alternative to prosthetic materials in the repair of large hiatal hernias. Additional clinical experience and prospective randomized trials are necessary to establish the proper role for the bioprosthetic repair of hiatal defects.

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