ORIGINAL RESEARCH

Tracheal reconstruction with porcine small intestine submucosa in a rabbit model

Samuel P. Gubbels, MD, Mark Richardson, MD, Dennis Trune, PhD, Daphne A. Bascom, MD, PhD, and Mark K. Wax, MD, Portland, Oregon; and Cleveland, Ohio

OBJECTIVE: To evaluate the ability of porcine small intestine submucosa (SIS) to 1) maintain airway patency, 2) integrate, 3) prevent granulation tissue formation, and 4) permit mucosalization when used for tracheal reconstruction. Further studies were performed to evaluate the ability of SIS to support neochondrogenesis and investigate the impact of neochondrogenesis on airway patency.

STUDY DESIGN: Prospective, controlled animal trial with SIS used with and without a perichondrial flap to reconstruct a tracheal defect in a rabbit model. Functional, histologic and endoscopic analyses were performed.

RESULTS: All animals except 1 control animal were without stridor. The SIS graft supported neochondrogenesis, was completely mucosalized and was well integrated into the neotrachea. There was minimal granulation tissue formation. Endoscopic analyses did not reveal a consistent, significant difference in airway patency when SIS, with or without a perichondrial flap, was used for reconstruction.

CONCLUSION: SIS can be used to reconstruct a sublethal rabbit tracheal defect with no mortality and minimal morbidity.
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Partial or complete stenosis of the trachea is usually due to complications of endotracheal intubation, tracheostomy, or external trauma. Many different methods of management of this problem have been described, the majority with good long-term success rates. However, there exists a subset of patients with severe tracheal stenosis that standard methods of reconstruction prove unsuccessful. The treatment of this type of severe stenosis has prompted research into the development of many new surgical techniques of open reconstruction.

Kimura et al[1] described a technique for treatment of tracheal stenosis that involved splitting the anterior wall of the trachea with placement of a costal cartilage graft. Complications of this technique included anastomotic breakdown, stenosis, and granulation tissue formation. Another technique used for treatment of tracheal stenosis involves segmental resection with primary anastomosis. In a large series by Grillo and Zannini,[2] good results were obtained in 17 of 20 patients with this technique. Complications included anastomotic breakdown, stenosis, granulation tissue formation, and the need for postoperative intubation or tracheostomy. Other techniques such as wedge resection and tracheal homograft transplantation have been used with success in some series.[3-5]

Many groups have investigated the use of bioabsorbable stents for use in open reconstruction with mixed results. Complications have included wound breakdown, stent migration, mucous plugging, granulation tissue formation, stenosis, and high attrition rates (20% to 67%).[6-9]

The ideal grafting material for tracheal reconstruction should 1) provide adequate structural support to maintain airway patency without the need for a luminal stent, 2) integrate into the recipient tissue to avoid the need for removal, 3) produce minimal inflammatory response to avoid scar formation and stenosis, 4) rapidly mucosalize to allow for improved mucociliary transport and 5) be readily

available. One material that shows promise is porcine small intestine submucosa (SIS, Cook Biotech, Lafayette, IN). SIS is a rigid, cell-free collagen matrix that consists of 90% protein and 10% lipid and has been processed to remove immunogenic factors. This material has been used in sheet form in multiple in vivo settings as a graft material including bladder[10] and urethra[11] reconstruction, heart valve replacement,[12] diaphragmatic defect repair,[13] abdominal wall defect repair,[14] and regeneration of meniscal tissue.[15] The material is also supplied in a cylindrical form, which has been used as both a venous and arterial vascular graft. Histologic evaluation has demonstrated the materials ability to allow for complete epithelialization and mesenchymal cell infiltration with ingrowth of a robust microvascular network.[13] Sandusky et al[16] found the material to increase in size with growth of the recipient animal when SIS was used as a venous interposition graft. These findings demonstrate that the material can act as a scaffold for site-specific remodeling while not imposing limitations on overall growth of the tissue.

The objectives of this study were to evaluate the ability of SIS to maintain airway patency, integrate into the tracheal wall, avoid granulation tissue formation, and allow for mucosalization with respiratory epithelium when used to reconstruct a tracheal defect. In addition, the potential for SIS to support new cartilage formation and the impact of the formation of a layer of cartilage on airway patency were evaluated.

METHODS

Twenty-five adult New Zealand white rabbits weighing 3.5 to 4.5 kg were used as subjects (Fig 1). The study protocol was approved by the Oregon Health & Science University animal care and use committee.

Operative Procedures
The subjects were induced with a subcutaneous injection of a ketamine-based anesthesia cocktail. After shaving of neck
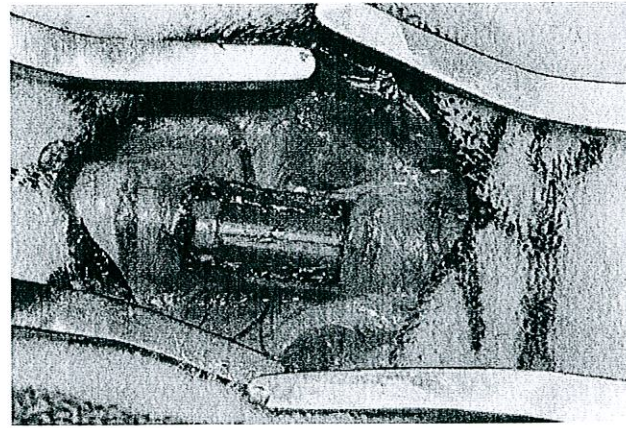
Figure 1 Study design.

Figure 2 Tracheal defect created in all animals.

and ear fur, an infusion of lactated ringers solution was started through an IV placed in the dorsal central auricular vein of the left ear. A fluoroquinolone antibiotic was administered intravenously. The rabbits were intubated with a 3.0 cuffed oral endotracheal tube (ETT). The animals were then placed supine and given an inhalational anesthetic. The animals ventilated spontaneously throughout the procedure. Oxygen saturation, end-tidal CO2, and heart rate were monitored during surgery.

A vertical, midline incision was made over the larynx and trachea. The strap muscles, thyroid, and investing fascia were dissected and retracted laterally, providing wide exposure to the airway. The position of the ETT cuff was verified to be distal to the site of the proposed defect. A 3-ring, 180-degree anterior tracheal wall defect was then made in tracheal rings 3-5 (Fig 2). The average defect size was 4 mm in width by 11 mm in length.

Control Animals
Five animals (control group) underwent no tracheal reconstruction after creation of the defect. The cervical incision was closed in these animals in 2 layers with absorbable sutures after securing a 5 × 2 mm penrose drain in the inferior aspect of the incision. The strap muscles were not sutured together in the midline on closure.

SIS Reconstruction
Ten animals had reconstruction of the tracheal defect with SIS (SIS group). An 8-layer vascular SIS stent was bisected to produce a 180 degree curved prosthesis that was trimmed to allow for 1 to 2 mm of overlap externally beyond the edges of the tracheal defect (Fig 3). This was secured circumferentially using 6-0 Biosyn. A penrose drain was placed and closure performed as with the control animals.

Auricular Perichondrial Flap and SIS Reconstruction
Ten animals had reconstruction of the tracheal defect with the SIS graft (as above) along with a pedicled auricular
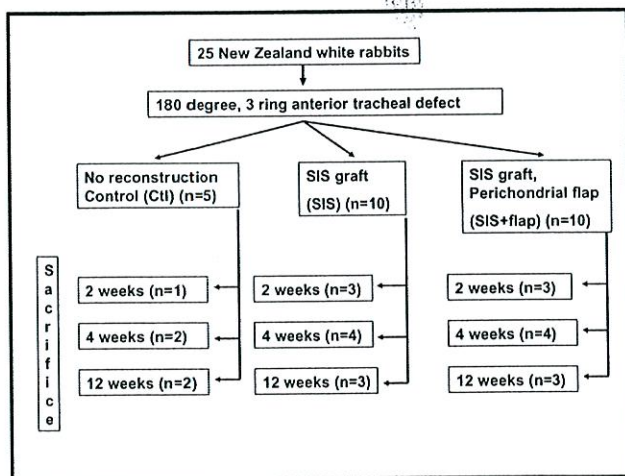
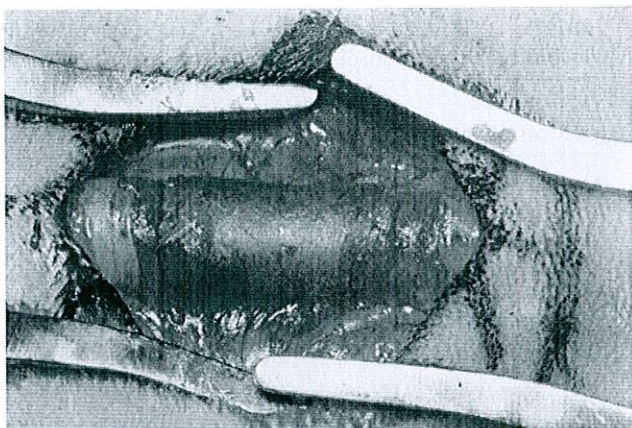**Figure 3** Tracheal defect reconstructed with SIS graft. The graft overlapped the edges of the defect by 2 TO 3 mm on all sides.

Figure 4 Pedicled auricular perichondrial flap sewn in place over SIS graft. Nine absorbable tacking sutures were used to secure the flap to the SIS graft. The pedicle can be seen just above the flap.

perichondrial flap (SIS + flap group). A 2 cm wide circular dermoperichondrial flap was raised from the distal third of the dorsum of the right ear. This flap was based on the dorsal central auricular vascular bundle, which was isolated down to the level of the root of the helix. A subcutaneous tunnel from the ear to the midline was made and the flap and pedicle passed through it. The auricular perichondrial flap was then sewn into place on top of the SIS graft using 9 tacking stitches of absorbable suture (Fig 4). The cervical skin was then closed in 1 layer incorporating the skin paddle of the perichondrial flap into the closure so as to allow for postoperative monitoring of flap viability. A small penrose drain was placed in the inferior aspect of the incision. The remaining cartilage and overlying ventral auricular soft tissue was excised from the ear and the skin of the auricular donor site was closed with absorbable suture. Bacitracin ointment was applied to all incisions. The animals were awakened and extubated immediately after closure.

Postoperative Care

Animals were monitored closely in the immediate postoperative period. When stable, animals were placed into cages and monitored twice daily. Monitoring included observation of level of activity, oral intake, presence of stridor or respiratory distress, flap viability (where indicated), wound status, and temperature. All drains were removed on postoperative day (POD) 6. All animals received 5 days of a subcutaneous fluoroquinolone antibiotic and 3 days of a subcutaneous narcotic analgesic.

Airway Evaluation

Of the 5 animals in the control group, 1 was euthanized at 2 weeks postoperatively, 2 at 4 weeks postoperatively and 2 at 12 weeks postoperatively. Of the 10 animals in each of the SIS and SIS + flap groups, 3 were euthanized at 2 weeks postoperatively, 4 at 4 weeks postoperatively, and 3 at 12 weeks postoperatively.

Animals were given a subcutaneous injection of a ketamine-based anesthesia cocktail before euthanization with
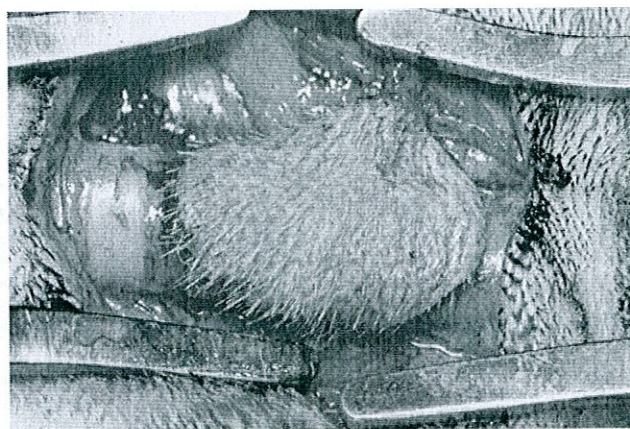
an intracardiac injection of a pentobarbital-based euthanasia solution. Immediately after sacrifice, bronchoscopy was performed with a 4.0 mm 0 degree rigid endoscope. Multiple images were taken of each animal's airway with a digital camera attached to the rigid endoscope. The reconstructed airway segments were then harvested and placed into fixative (1.5% paraformaldehyde–3% glutaraldehyde in 0.1 M PO4 buffer).

The images were compiled digitally and reviewed by 2 experienced otolaryngologists (MAR, MKW) blinded to the method of reconstruction. Endoscopic images of normal rabbit airways were included in the series of images and as a negative control. Airways were graded for maximal degree of stenosis: Grade I, 0 to 33% stenosis; Grade II, 33% to 66% stenosis; Grade III, 66% to 100% stenosis (Figs 5 and 6).
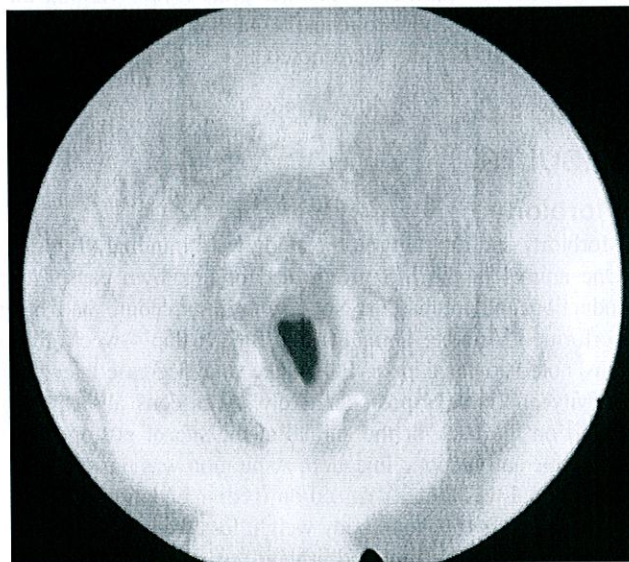

Figure 5 Endoscopic image of a control animal at 2 weeks demonstrates grade 3 stenosis (67% to 100%).
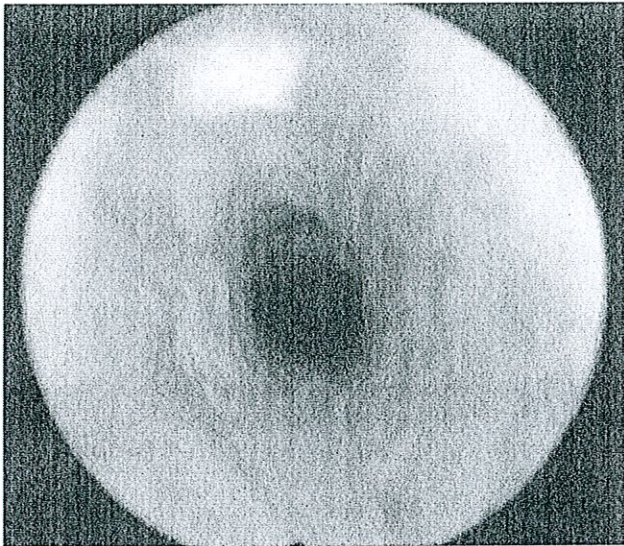
Figure 6 Endoscopic image of a SIS animal at 2 weeks demonstrates a grade 1 stenosis (0 to 33%). Compare with Figure 5.

Table 1
Morbidity: Study complications by group

Complication	SIS (n = 10)	SIS + flap (n = 10)	Control (n = 5)
Stridor	0	0	1
Auricular hematoma	N/A	3	N/A
Distal auricular necrosis	N/A	1	N/A
Flap failure	N/A	0	N/A
Flap separation	N/A	1	N/A
Infection			
Wound	0	0	0
Distant	0	1*	0
Death			
Anesthesia-related	1†	0	0
Surgical	0	0	0

*Abscess on back of animal at narcotic/antibiotic injection site. Subject sacrificed and replaced in study group.
†Arrest on intubation, induction. No surgery performed. Subject sacrificed and replaced in study group.

Responses were evaluated for consistency between reviewers and analysis of variance performed to compare the 3 groups of subjects (SIS, SIS + flap, control). Univariate analysis of variance with post hoc planned comparisons were used to compare the responses of each evaluator individually as well as the average of the 2 grades assigned for each animal.

HISTOLOGIC EVALUATION

Harvested airways were fixed, dehydrated and embedded in plastic then sectioned at 5 μm. Sections were then serially mounted on glass slides, stained, and evaluated microscopically for completeness of mucosalization, presence of granulation tissue, number of distinct graft layers visible, and presence of neochondrogenesis. Qualitative differences in the pattern of healing were noted.

RESULTS

Morbidity
Morbidity and mortality in the study were minimal (Table 1). One animal in the SIS group died of unknown cause after induction and intubation. No operative procedure had been performed. Another animal in the SIS + flap 4-week group was noted to have poor PO intake and decreased level of activity at 2 weeks postoperatively. A caseous abscess was found on the back of the animal at the site of postoperative antibiotic and narcotic injection. Aspiration was unsuccessful. The animal was then sacrificed on recommendation of veterinary staff as a 15% total body weight loss was noted. Both of these subjects were replaced in their respective study groups.

Three of the 10 animals in the SIS + flap group developed auricular hematomas, which were treated with warm compresses. One of the 10 animals in the SIS + flap group was found to have necrosis of the distal 1 to 2 cm of the donor auricle that was treated with antibiotic ointment.

There were no flap failures. One animal in the SIS + flap 12-week group had separation of the flap from the SIS graft evident at necropsy.

All animals were extubated successfully without operative complications. All animals had a period of transient stridor/stertor after extubation that resolved by 3 hours postoperatively. Beyond 3 hours postoperatively, all animals except 1 were without stridor or respiratory distress and resumed normal activity and oral intake by POD 2. One subject in the control group did develop slowly progressive stridor postoperatively but survived until the predetermined 2 week date of sacrifice.

Airway Evaluation
A univariate analysis of variance revealed a significant relationship (F = 5.544, P = 0.015) between treatment groups for 1 of the blinded evaluators. Post hoc planned comparisons showed statistically significant differences for the SIS and SIS + flap groups compared with the control group with an average 0.7 and 0.6 lower score (less stenotic) than the controls (P = 0.015 and P = 0.038, respectively).

A similar analysis of the second evaluator's ratings did not indicate statistically significant differences between the treatment groups, (F = 1.301, P = 0.300). For both evaluators, time of rating was not a significant factor within or between groups. Ratings by the 2 evaluators were then averaged for each animal. A univariate analysis of variance of the averaged ratings did show a significant difference (F = 4.001, P = 0.039) between groups. Further post hoc comparisons, however, revealed no significant difference between the SIS or the SIS + flap groups compared with the

Table 2
Endoscopic analysis: Post hoc planned comparisons. Mean difference in airway score: group average of all time points

Group comparison	Evaluator 1	Evaluator 2	Combined evaluators 1 and 2
SIS versus control	−0.70 ($P = 0.015$)	−0.40 ($P = 0.586$)	−0.55 ($P = 0.090$)
SIS + flap versus control	−0.60 ($P = 0.038$)	−0.40 ($P = 0.586$)	−0.50 ($P = 0.130$)
SIS versus SIS + flap	−0.10 ($P = 0.845$)	0.00 ($P = 1.00$)	−0.05 ($P = 0.966$)

control group ($P = 0.130$ and $P = 0.090$, respectively) (Tables 2 and 3).

There was no statistical significance noted between the ratings assigned for the SIS and the SIS + flap group in any of the analyses ($P < 0.050$ in all analyses).

A calculation of the effect sizes between groups was performed to enable a power analysis of the data. When comparing the SIS group to the controls an effect size of 1.17 was found; comparison of the SIS + flap group to the controls produced an effect size of 1.16. Assuming a P value of 0.05 and a power of 0.95, a group size of 16 would have been needed to correctly detect a difference.

HISTOLOGIC FINDINGS

Histologic slides were evaluated for mucosalization, graft integration, granulation tissue, and neochondrogenesis (Table 4). Mucosalization was graded on the percentage of airway lumen mucosalized (based on the section that showed the least amount of mucosalization for that animal). At 2 weeks, all groups showed incomplete mucosalization with 50% to 75 % of the axial airway lumen mucosalized (defect was 50% of lumen). By 4 weeks, all of the control animals and 50% (range, 50% to 100%) of both reconstructed groups were completely mucosalized. All groups were completely mucosalized by 12 weeks with the exception of 1 SIS animal (Fig 7).

Granulation tissue was present in almost all animals at 2 weeks. By 4 weeks, half of the reconstructed (SIS and SIS + flap) and none of the control animals had granulation tissue. Granulation tissue had resolved in all animals by 12 weeks except for 1 animal in the SIS group.

Layers of the SIS graft were counted on the histologic sections to determine how many of the original 8 layers

remianed. At 2 weeks, 4 to 6 layers of the graft were visible in all animals (Fig 8). At 4 weeks, 3 to 4 layers of the graft were visible in most of the animals in the SIS and SIS + flap groups (range, 0 to 4). No graft material was visible in any of the animals at 12 weeks.

A small area of new cartilage was visible in only 1 of the SIS + flap animals at 2 weeks. By 4 weeks, a thick centrally located plate of new cartilage was visible in all SIS + flap animals. Two of 3 (66%) SIS + flap subjects at 12 weeks had a thick and more mature appearing plate of cartilage. One of the 12-week SIS + flap animals was found to have dehiscence of the auricular perichondrial flap from the SIS graft with no neochondrogenesis visible.

A qualitative difference in the pattern of healing was evident on histologic comparison of the reconstructed airway segments (SIS and SIS + flap) to controls. There was a more constricted appearance in the control groups with a more acute angle and increased submucosal fibrovasular evident at the apex (anterior aspect) of the airway (Fig 9). The animals that had SIS graft reconstruction, with or without a perichondrial flap, demonstrated a more rounded, obtuse apical angle with minimal submucosal tissue (Fig 10). The reconstructed airways did not have the constricted appearance seen in the control animals where the remaining native cartilage sidewalls had healed in closer approximation.

DISCUSSION

The search for novel methods of treatment for tracheal stenosis has led many groups to investigate the feasibility of using engineered tissue to reconstruct airway defects. Clevens et al[17] used an auricular perichondrial graft to reconstruct a cricothyroid membrane defect in a rabbit model. A segment of endotracheal tube was used as an internal

Table 3
Endoscopic analysis: Analysis of variance of average airway scores for reconstructed versus nonreconstructed (control) subjects by evaluator

	Evaluator 1	Evaluator 2	Combined evaluators 1 & 2
SIS reconstruction* versus no reconstruction	F = 5.544 ($P = 0.015$)	F = 1.301 ($P = 0.300$)	F = 4.001 ($P = 0.039$)

*With or without auricular perichondrial flap.

Table 4
Histological analysis: Group average histologic findings at 2, 4, and 12 weeks

Timepoint/ group	Mucosalization* (Percentage of axial airway)	Granulation tissue† (Percentage of subjects)	Graft resorbtion (Number of graft layers visible‡)	Neochondrogenesis (Percentage of animals with new cartilage deposition)
2 weeks				
Control	50	100	N/A	N/A
SIS	50	66	5.6	N/A
SIS + flap	66	100	4.6	33
4 weeks				
Control	100	0	N/A	N/A
SIS	85	50	2.6	N/A
SIS + flap	81	50	2.5	100
12 weeks				
Control	100	0	N/A	N/A
SIS	96	33	0	N/A
SIS + flap	100	0	0	66

*Defect was approximately 50% of lumen.
†Percentage of subjects with granulation tissue present.
‡Original graft was 8 layers.

stent during the healing process. Approximately one quarter of the subjects developed fatal mucous plugging. Naficy et al[18] showed that a vascularized perichondrial graft could be used to reconstruct a 2-ring, 270-degree tracheal defect in a rabbit model. An intraluminal stent was again used with an overall mortality rate of approximately 25% and complications of granulation tissue formation and mucous plugging.

The use of an intraluminal stent presents multiple problems both in the experimental model and in its application to the clinical setting. Intraluminal stenting can be complicated by mucous plugging, granulation tissue formation, stent migration, and airway obstruction.[17] These complications, in addition to the need for stent removal, have led surgeons to seek alternative reconstruction methods.

An active area of investigation involves the use of absorbable stents for tracheal reconstruction. These types of stents are designed to be placed either internally (intraluminal) or externally and avoid the need for later stent removal. Robey et al[6] used an internal bioabsorbable stent made of poly(D,L-lactide-co-glycolide) (PLGA) in a rabbit model with a 3.5 × 15 mm elliptical tracheal defect. In the experimental animals, the stents were placed with a fascialata graft whereas control animals had reconstruction with fascialata alone. The stented group had stridor and attrition rates of 17% and 17%, respectively, compared with 38% and 23% for the control group. When the same material was used as an external stent,[7] the death rate in the experimental group was 50% versus 23% for the control group. Another study[8] used bioabsorbable plates made of Lactosorb as stents in both external and internal
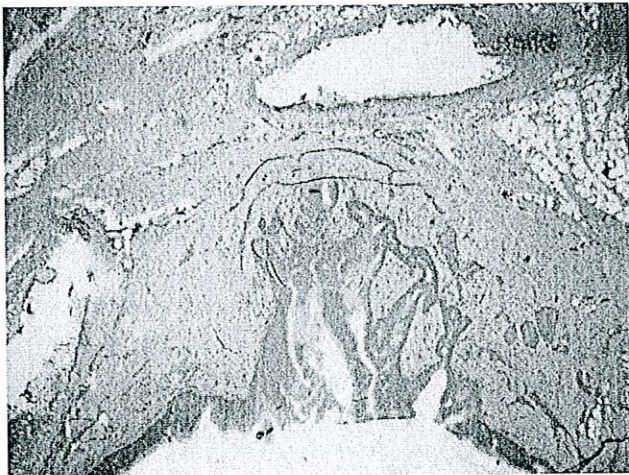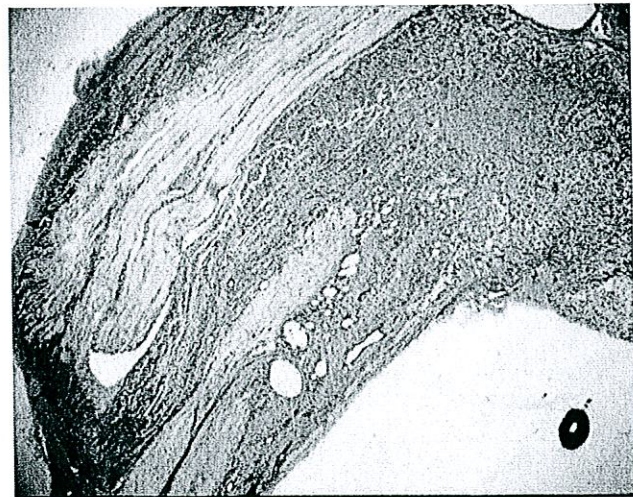

Figure 7   Complete mucosalization of tracheal defect reconstructed with SIS graft and perichondrial flap shows well-developed associated glandular structures. Preservation artifact affects the cartilage sidewalls and newly deposited cartilage above.

Figure 8   SIS graft at 2 weeks. Absorption of only the peripheral graft layers has taken place.
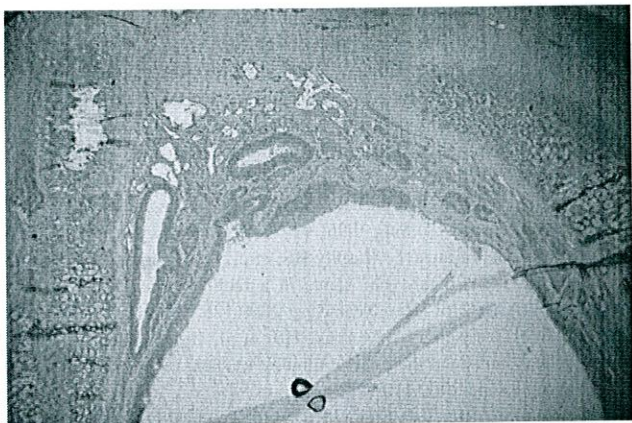
Figure 9 Airway defect reconstructed with SIS at 12 weeks. The apical aspect has minimal submucosal soft tissue. Compare with Figure 10.

fashion for tracheal reconstruction in a porcine model with a 5-ring vertical anterior tracheal wall incision. They found that the stent absorbed with minimal scar or granulation tissue formation when placed externally, though the mortality rate in this group was 33%. When placed internally the mortality rate was 75% as the stent was found to break down, migrate distally, and cause consolidation in the lungs.

In the current study, there was no surgical mortality and minimal morbidity. All animals who underwent reconstruction of the tracheal defect and most (4 of 5) of the animals who had no reconstruction were clinically normal (activity, diet) and without stridor postoperatively. Because the defect used in the current study was clearly a sublethal defect, there was no survival benefit seen between the control and reconstructed animals. Other similar studies have used smaller defects and had higher rates of surgical complications and death. Critical to further animal research in tracheal reconstruction is the need to include a negative control in all investigations (creation of defect without reconstruction). The difference between a lethal and sublethal sized defect is unclear in animal studies and must be demonstrated directly (not assumed) for accurate conclusions to be drawn.

The addition of a perichondrial flap to reconstruction with SIS did not result in any significant improvement in airway patency. On histology, almost all of the animals that had reconstruction with a perichondrial flap had growth of a cartilaginous plate on the SIS graft, though the presence of the cartilage did not seem to add any structural advantage to the reconstruction. This is likely because the cartilage was deposited too late in the healing process to provide stenting action for improved airway patency. Perhaps staged reconstruction of the tracheal defect using the perichondrial flap after the cartilage plate has been deposited would yield an improved airway result.

The results of the endoscopic evaluation in this study did not reveal a consistent improvement in airway patency with SIS reconstruction. The results of one evaluator did show a

significant improvement in the airway patency, whereas the second evaluator's ratings did not. A power analysis based on the effect sizes showed a need for approximately 16 animals in each of the 3 groups to be able to correctly detect a difference between them. Because of this, it is difficult to determine whether the significance, or lack thereof, seen in our endoscopic analysis is accurate or represents a Type II or Type 1 error, respectively. Larger numbers of animals in each group may have revealed a more consistent improvement in airway patency when SIS was used for reconstruction, as suggested by the significance of the first evaluator's ratings and the trend toward significance seen when the 2 evaluators scores were analyzed together.

On histological analysis of the reconstructed segments, SIS did posses many qualities desirable in a tracheal stent. Complete graft integration and epithelialization with a robust respiratory mucosa and accessory glands occurred by 12 weeks in most subjects. Granulation tissue had resolved in most subjects by 12 weeks. The use of SIS for posterior tracheal grafting or external grafting of small, anterior tracheal wall defects was not evaluated in this study, though its profile of biomechanical properties may prove useful in these situations.

The significance of the qualitative differences seen in the pattern of healing between the reconstructed (SIS and SIS + flap) and the control animals is unclear. The constricted pattern of healing suggests a higher degree of stenosis in the control animals; though this did not clearly result in decreased airway patency as evaluated by endoscopy. One limitation of our study was the method of evaluation of airway patency that was used. Endoscopic evaluation with grading of airway patency does not quantify the minimal airway diameter and length of the stenosis. Some studies have used direct measurement of airway diameter on histo-
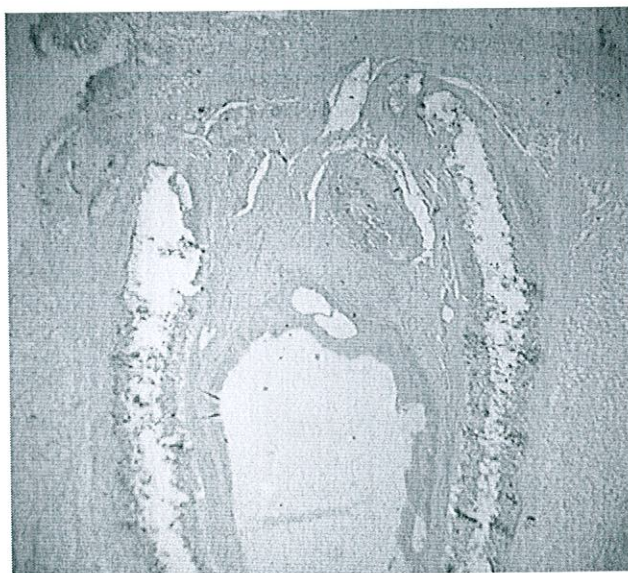

Figure 10 Control animal at 4 weeks. Abundant submucosal soft tissue is visible at the apex of the reconstructed defect. Compare with Figure 9. Preservation artifact affects cartilage sidewalls.

logic sections to quantify airway patency. In the current study, there was a large difference in the size of the harvested specimen between the reconstructed and control animals. This resulted in a variable amount of shrinkage that occurred on histologic processing of the specimen from the 3 groups. Because of this, direct measurement of airway diameter on histologic sections was found to be an inaccurate means of assessing airway patency. The use of plaster casts with subsequent morphometrics or possibly a balloon catheter technique would likely provide the most accurate means of assessing airway patency. These techniques were not used in the current study as they can cause disruption of the mucosa or any granulation tissue that may be present and potentially have interfered with histologic assessment of the specimen. Because of this, an endoscopic technique was used. Despite this, both of the evaluators did correctly identify all of the normal airways that were included on the series of endoscopic images as grade 1 (0 to 33%) stenosis, and overall had correlation of the grades between them in 70% of subjects, indicating a good accuracy in the evaluation of stenotic airways.

CONCLUSIONS

Porcine small intestine can be used to reconstruct a sublethal tracheal defect in a rabbit model with no mortality and minimal morbidity. In this role, SIS completely mucosalizes, integrates into the surrounding tissue, and has minimal granulation tissue formation. SIS can support neochondrogenesis when a vascularized perichondrial flap is used.

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