Dynamic Tissue Expansion of the Larynx in a Canine Model

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Objectives: To test whether staged, progressive, monitored, dynamic tissue expansion is possible in the larynx and to evaluate its effectiveness in dilating and augmenting constricting cicatricial lesions.

Design: Animal study.

Setting: Research facility, tertiary care medical center.

Subjects: Thirteen dogs, 3 with laryngotracheal stenosis.

Interventions: Dogs underwent laryngeal splits, tracheostomy, and insertion of inflatable stents. In 7 normal dogs, stents were progressively inflated by air in predetermined increments during 11 days. In 3 normal dogs and 3 with laryngotracheal stenosis, stents were gradually expanded by water. Stents were kept in place for 21 days. After removal, dogs were observed for 25 days. Five died of complications of tracheostomy.

Main Outcome Measures: Airway diameter measured by endoscopy before the induction of stenosis, before the laryngeal splitting procedure, after stent removal, and before euthanasia.

Results: The lumen increased, then shrank somewhat after stent removal. In 2 surviving dogs with laryngotracheal stenosis and water-expanded stents, the lumen was 82.5% larger than baseline at stent removal and 71.0% larger at euthanasia. In 2 surviving normal dogs with water-expanded stents, lumen size increased by 50.0% at stent removal, and in 1 dog surviving to day 46, it was 17.0% larger. In 5 surviving dogs with air-inflated stents, lumen size was 39.0% larger at stent removal and 8.0% larger at day 46. Histologically, fibrous tissue developed in the gaps between the splayed margins of the laryngeal cartilages.

Conclusions: The larynx may be dynamically expanded. Although the maximal diameter is not maintained, final cross-sectional areas are larger.


LARYNGOTRACHEAL stenosis (LTS) may be congenital or acquired. The incidence of LTS has increased over the years because of improved health care of premature intubated infants, patients receiving prolonged assisted ventilation, and patients with trauma, chronic illness, and/or cancer.1 Stenoses of more than 70% of the lumen diameter at any level of the airway are usually clinically restrictive and often must be surgically treated.2 Managing such stenoses is quite complicated. An adequate stable airway must be established without jeopardizing other laryngeal functions, such as airway protection, speech, and coughing. Despite the availability of various surgical treatment options for LTS, none produces completely satisfactory results.

Tracheotomy bypasses the stenotic area. It may be complicated, however, by plugging, decannulation, infection, and even death. It may also further damage the already impaired airway and compromise quality of life. Decannulation and closure are therefore important goals in the treatment of LTS.3

Endoscopic techniques for treating LTS include dilatation with bougies or with rigid bronchoscopes combined with instrumental removal of scar tissue or laser ablation. After surgery, stenosis tends to recur and often worsens. Many patients require numerous procedures before the stenosis can be resolved.4,5

Open surgical laryngotracheal reconstruction is often more effective than endoscopic dilatation and is indicated whenever the laryngeal skeleton is involved in the stenosing process, or when there is weakening (malacia) and collapse of the skeletal framework. Postoperative intraluminal stenting may be used to support the airway from within, bolster grafts and flaps, and maintain the lumen during heal-

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MATERIALS AND METHODS

The study was approved by the Animal Research Committee of the Cleveland Clinic Foundation, Cleveland, Ohio, and the animals received humane care in compliance with the Principles of Laboratory Animal Care formulated by the National Society for Medical Research and the Guide for the Care and Use of Laboratory Animals prepared by the National Academy of Sciences.

Thirteen mongrels (Canis familiaris), each weighing between 10 and 12 kg, were divided into 3 study groups (Table 1). The study protocol is shown in Table 2.

The stent was designed by one of us (I.E.) and produced and developed at Hood Laboratories Inc (Pembroke, Mass). It is made of biocompatible medical-grade silicon, is easily inserted, and, when in place, is retained in position by conforming with the intralaryngeal configuration. Once inflated it is secured and stabilized in its position. Air pressures within the stent can be carefully monitored and adjusted with a digital pressure-volume gauge attached to a 1-way valved Luer connector. A thin flexible tube extends from the Luer connector into the lower pole of the stent. However, silicon may leak air, so the stent may also be expanded with water. When water is used, the stent is inflated to the same volume as when air is used.

INDUCTION OF LTS

Laryngotracheal stenosis was induced in 3 dogs by a previously proved technique.12 Each dog was anesthetized with intramuscular ketamine hydrochloride (20 mg/kg) and intramuscular xylazine hydrochloride (1.5 mg/kg) and placed in the supine position with its mouth kept open with a bite block. The tongue was extended and the exposed larynx sprayed with topical anesthetic spray (Cetacaine; Cetylite Industries Inc, Pennsauken, NJ). The epiglottis was lifted with the tip of a 3.5-mm 30° telescope (Hopkins; Karl Storz Endoscopy, Culver City, Calif), connected through a video camera to a monitor. The junction between the lower part of the cricoid cartilage and the upper part of the first tracheal ring was traumatized by electrocautery with a curved insulated suction-cautery tip connected to a standard Bovie electrosurgical cautery system and operated at 40 power units. The mucosa and underlying cartilage were injured at 4 equally spaced points, with the use of 2- to 3-second exposures. The dogs were then observed for 14 to 16 days, during which all 3 developed LTS restricting the airway by more than 70%.

LARYNGEAL SPLIT, LONG-TERM TRACHEOSTOMY, AND INSERTION OF STENT

Each dog was anesthetized with intravenous pentobarbital sodium (25-30 mg/kg). A No. 6 tube was introduced through the mouth and advanced under endoscopic guidance into the trachea. The anterior part of the neck was then shaved, a circular area of skin overlying tracheal rings 5 to 10 and measuring 5 cm in diameter was excised, and the margins were vastly undermined. The strap muscles were separated and sutured sideways. The anterior cartilaginous skeleton of the laryngotracheal complex was split in the midline from below the vocal cords to the second tracheal ring. Care was taken to preserve the mucosa. In animals with previously established stenosis, scar tissue was split as well down to the mucosa, which was left intact.

By means of a previously described technique,13 a permanent tube-free, self-sustaining tracheostomy was then performed. Before the upper skin flap of the tracheostomy was sutured, the inflatable stent was inserted through the stoma (Figure 1) under endoscopic guidance. It was secured in its position by means of a suture passed through the petiole of the epiglottis, and by passing the flexible inflating tube through the anterior tracheal wall and the skin. The upper skin flap was then sutured to the trachea and a temporary tracheotomy tube was placed to ventilate the animal until it fully recovered from the general anesthetic. The tube was removed when spontaneous ventilation was re-established, and the dogs remained tube free throughout the study period.

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DYNAMIC EXPANSION

Postoperatively, study subjects received acetaminophen, 10 mg/kg, when required to control pain. Daily suctioning and routine local care of the wound were provided for the tracheostomy site. Two methods were used to dynamically expand the laryngeal lumen.

1. In groups 1 and 2, the stent was initially filled with 6 mL of water. Then, 0.2 mL was added every other day until the stent was filled with a total of 7 mL of water. This volume was previously found to be equal to the volume of the maximally air-inflated stent.

2. In group 3, the stent was gradually inflated with air during a period of 11 days. Starting at a pressure of 30 mm Hg, the pressure of the stent (and thus its volume) was adjusted gradually every 2 days until a pressure of 40 mm Hg was achieved (intraluminal stent pressure should not exceed the physiologic arteriolar blood pressure of approximately 40 mm Hg). The air pressure within the balloon was monitored manometrically twice daily.

The stent was left in its place in its maximally expanded or inflated state for 10 more days, to promote healing of the larynx in the desired dimension. During the whole period, the dogs received adequate oral nutrition and local tracheostomy care. Twenty-one days postoperatively, the stent was removed with the animal under general anesthesia, and the expanded laryngeal airway diameter was measured and documented.

ENDOSCOPIC EXAMINATION
AND VIDEO DOCUMENTATION

Endoscopic examinations with video documentation were performed before the induction of stenosis, before the laryngeal splitting procedure, after stent removal, and before the animals were euthanized. To ensure consistency in measurements, the tip of the telescope was always positioned at the plane of the free edges of the true vocal cords. The videotaped examination was reviewed in a computerized laboratory by means of Adobe Photoshop 4.0 and Illustrator 6.0 software (Adobe Systems Inc, San Jose, Calif).

Five dogs died at some point during the study of complications of the tracheostomy. Unfortunately, dogs do not tolerate the establishment of a tracheostomy (because the cannula induces substantial secretions and can become occluded or dislodged) or of a tracheostomy (because the surrounding skin and fur may collapse and occlude the stoma, or the stoma may gradually constrict). Too many dogs are therefore lost. However, the canine model was chosen in the current study because the canine's laryngotracheal complex is similar to the human region in anatomy, vasculariy, innervation, and physiologic features. It is therefore the most widely used and comparable model.

The mean percentage change from the initial cross-sectional area in the surviving dogs is shown in Table 3. An example of consecutive endoscopic examinations of 1 dog is shown in Figure 2.

On 3-dimensional computed tomography performed during the stenting period (Figure 3) and on pathological examination performed at the completion of the study (Figure 4), a wide gap between the free margins of the expanded cricoid and thyroid cartilages was found. Fibrous tissue bridged this expanded wide gap (Figure 5). Only a small amount of granulation tissue, predominantly caused locally by the retaining suture, was found at stent removal, and in all cases it was spontaneously resolved by the time of death (Figure 2). There were no signs of perichondritis or of cartilage necrosis.

The larynx is a hollow tube made of a cartilaginous skeleton. The lumen cannot be expanded beyond the natural diameter without splitting the cartilaginous skeleton. In laryngotracheal reconstruction procedures, the stenotic laryngeal segment may be split anteriorly, posteriorly, laterally, or in combinations of the above. Widening and stability of the lumen are maintained by interpositioned grafts, by a stent, or by both. Most
reconstructive techniques rely on autologous rib or nasal septal cartilages for expansion. Harvesting these cartilages, however, requires additional surgical procedures that must be performed on a separate location away from the laryngotracheal surgical field. These cartilages may also be displaced, rejected, or infected. Extended or prolonged periods of postoperative stenting with the tracheotomy tube in place are usually required, which increases the risks of complications or failures.20,21

For chronic gradual tissue expansion, a distensible implant is used to encourage growth of additional tissue. Skin has been the primary target of long-term tissue expansion because it expands in response to tension, and because it readily synthesizes new connective tissue. However, tissue expanders have also been used with success in animal models to lengthen peripheral nerves, ureters, and small bowel.10,22,23 We therefore presumed that a staged, progressive, incremental dynamic tissue expansion, combined with splitting of the laryngeal skeleton and preservation of intact internal mucoperichondrium, would allow gradual expansion of the skeleton and the mucosa without pressure-induced tissue necrosis. Eventually this might lead to permanent stable enlargement of the lumen, which may enable closure of a preexisting tracheotomy.

### Table 1. Experimental Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Subjects</th>
<th>Status of Larynx</th>
<th>Method of Stent Expansion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>Induced stenosis</td>
<td>Water</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>Normal</td>
<td>Water</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>Normal</td>
<td>Air</td>
</tr>
</tbody>
</table>

### Table 2. Experimental Protocol*<sup>1</sup>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Step</th>
<th>Group 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A. Preparation Day −16 to −14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Induction of laryngotracheal stenosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B. Treatment Day 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Endoscopy, measurements, and documentation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Laryngeal split</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Long-term tracheostomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Insertion and fixation of stent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C. Expansion Days 0-21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Gradual filling of stent with water (11 d) and plateau-like maximal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>filling in final predetermined volume, 3D CT (10 d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Stent removal (day 21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Endoscopy, measurements, and documentation (day 21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D. Healing process Days 21-46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Posttreatment observation, 3D CT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E. End of study Day 46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Euthanasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Measurements and documentation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Laryngectomy and pathological examination</td>
</tr>
</tbody>
</table>

### Table 3. Luminal Size Increases After Dynamic Tissue Expansion*<sup>2</sup>

<table>
<thead>
<tr>
<th>Group</th>
<th>Change From Baseline, % At Stent Removal (Day 21)</th>
<th>At Euthanasia (Day 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTS + water expansion (n = 3)</td>
<td>+82.5 (72.5-92.5) (n = 2)</td>
<td>+71.0 (62-80) (n = 2)</td>
</tr>
<tr>
<td>Normal larynx + water expansion (n = 3)</td>
<td>+50.0 (41-59) (n = 2)</td>
<td>+17.0 (n = 1)</td>
</tr>
<tr>
<td>Normal larynx + air inflation (n = 7)</td>
<td>+39.0 (32-51) (n = 5)</td>
<td>+8.0 (0-22) (n = 5)</td>
</tr>
</tbody>
</table>

LTS indicates laryngotracheal stenosis. Values are given as mean (range).

*3D CT indicates 3-dimensional computed tomography.

Figure 1. The inflatable stent is introduced through the tracheostoma. The level of the cricoid cartilage is marked on the right. The flexible tube used for inflation extends from the lower pole of the stent on the left.
We believe that the ideal laryngeal expanding stent should replicate the characteristics of the stent described in 1990 by Eliachar and Nguyen.\(^1\) It should be available in different sizes and shapes; it should be safe with no risk of airway obstruction; and it should not cause marked foreign-body reaction. It should be soft and smooth to avoid mucosal abrasion and pressure necrosis. Ease and safety of insertion and removal are mandatory. Stabilization and safe maintenance in position should be achieved by atraumatic means. A dynamic versatile stent with progressive expansile features should also be readily distensible at monitored rates.

The Eliachar laryngotracheal stent (Hood Laboratories Inc) provides internal laryngeal support and controls aspiration.\(^1\) Recently, a new inflatable, low-pressure, high-volume balloonlike stent was designed (Hood Laboratories Inc). It is flexible, thin-walled, and preformed to fit the inner contours of the larynx. In a canine model, it was safe and biocompatible, causing only minimal, reversible local tissue reaction.\(^{11}\) The air pressure inside the stent can be manometrically monitored to the finest degree and may be periodically adjusted by a readily available digital pressure-volume gauge. In its clinical human application, the stent is readily introduced, safely maintained in position without retaining sutures, easily monitored, and easily removed.

Figure 2. Consecutive endoscopic examinations of a dog with induced laryngotracheal stenosis and a stent expanded with water. A, Subglottic region before induction of stenosis. B, Laryngotracheal stenosis before balloon dilatation and laryngeal split (day 14). C, After stent removal (day 21). D, At day 46.

Figure 3. Three-dimensional computed tomography of a larynx containing an inflated stent. A gap of 9.76 mm between the free margins of the expanded cricoid cartilage is seen.
We therefore assumed that this stent could serve as a laryngeal tissue expander after an anterior laryngeal splitting procedure. The suggested tissue expansion process is as follows: (1) distention of the intact mucoperichondrium, (2) separation and spreading of the split cartilage skeletal segments, (3) ingrowth of fibrous tissue into the expanded gaps between the skeletal segments, and (4) overall stable and sustained expansion of the laryngeal skeleton and of its lumen. The staged, gradual, slow inflation of the stent is intended to avoid trauma caused by rapid expansion, which may result in pressure sores, inflammation, and scarring, with potential necrosis and eventual restenosis.

We propose the term safe splitting to describe longitudinal sterile section of the thyroid and cricoid cartilages down to but not through the intraluminal mucoperichondrium or the stenotic scar tissue. Safe splitting allows gradual stretching of the intact mucosa and internal perichondrium. Maintaining an intact membrane inside the larynx prevents pressure ischemic damage to the mucosa and reduces contamination and infection of the cartilage and surrounding soft tissue. In this preliminary study, we performed only anterior splits to maintain the integrity of the mucoperichondrium, which we had hoped would prevent complicating factors such as infection. Future studies might also incorporate lateral or posterior cricoid splits.

Air is the preferred medium for stent inflation and tissue expansion. It is less traumatic than water, being more flexible and shock absorbing. The stent used in this study is produced of silicon, which is known to leak air, albeit slowly. Therefore, the use of air for expansion was difficult, requiring frequent monitoring and reinflation. While possible in humans, it is a laborious task in the animal laboratory setting. Water is well retained by the new stent and is more consistent and reliable in achieving predictable expansion, but is potentially more traumatic to the surrounding tissue, being less flexible.

The results of our preliminary study clearly show that dynamic expansion is a viable option as a new treatment for LTS. Although the larynx does not maintain the maximal postexpansion diameter, the final cross-sectional area is larger than the initial pretreatment area. Our results suggest that stenotic larynges are particularly amenable to dynamic expansion. Water-filled stents seem to be more effective than air-filled stents but may be more traumatic. These factors should be carefully considered in future clinical applications. When expansion by water is attempted, the volume and pressure increments should be small and closely monitored. The proposed tissue expansion procedure may be used primarily or secondarily in conjunction with other procedures.
reconstructive treatments. It does not require the use of grafts, and the stenting period may be completed within 21 days.

**CONCLUSIONS**

This novel animal study suggests that the stenotic laryngotracheal complex may be dynamically expanded by specially designed stents. This opens up new opportunities in managing laryngotracheal stenosis. Further animal and human studies with longer observation periods and larger numbers are warranted.

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