Brief Report

Laryngeal Transplantation and 40-Month Follow-up

Marshall Strome, M.D., Jeannine Stein, M.D., Ramon Esclamado, M.D., Douglas Hicks, Ph.D., Robert R. Lorenz, M.D., William Braun, M.D., Randall Yetman, M.D., Isaac Eliachar, M.D., and James Mayes, M.D.

TOTAL laryngectomy and total occlusion of the larynx with tracheostomy are associated with an impaired sense of taste and smell, an increased incidence of tracheobronchial infections, stomal encrustations, loss of nasal respiration, and loss of a human-sounding voice. A fundamental consideration in treating a patient whose larynx has been irreparably damaged is whether the goals of surgery should include replacement of the larynx to improve the patient's quality of life. An early attempt to treat laryngeal cancer with a partial laryngeal transplant[1] was accompanied by rapid recurrence of the tumor, an outcome that quashed interest in the procedure for nearly two decades. Similarly, tracheal transplantation has had only limited success.[2,3]

In 1987, we initiated a program to explore the potential of laryngeal transplantation. The program addressed four issues critical to successful transplantation: revascularization, reinnervation, rejection, and the ethics of transplanting an organ considered by some to be nonvital. In rats, the rate of success of laryngeal transplantation was nearly 100 percent.[4,5] In these studies in animals, we classified the histologic features of laryngeal rejection[6]; determined the maximal tolerable period of ischemia; evaluated preservative solutions[5]; determined doses of cyclosporine,[7] prednisone, and adjunct in vitro radiation[8]; and studied the use of sirolimus and tacrolimus.[9]

In 1998, we performed a total laryngeal transplantation in a man who had sustained a severe traumatic injury to the larynx and pharynx.[10] We describe the procedure and report the results in detail here.

CASE REPORT

The Patient and the Donor

The patient was a 40-year-old man who had been in a motorcycle accident 20 years earlier. His larynx and pharynx had been crushed, leaving him aphonic. He lost his sense of smell and taste a year after the injury. He used an external device (Cooper-Rand Electrolarynx) to speak. Despite attempts at another institution to reconstruct his larynx, it was totally stenotic and shortened, with immobile arytenoid cartilages and a fragmented cricoid cartilage. A barium swallow revealed narrowing of the pharynx and upper esophagus and a pharyngolaryngeal fistula. The supraglottis was bathed in oropharyngeal secretions.

Other than mild essential hypertension that was treated with valsartan and hydrochlorothiazide, the patient was healthy. Although he had mild dysphagia, his nutritional status was normal. He did not smoke. Serologic tests for cytomegalovirus and Epstein–Barr virus were negative, and his serum creatinine concentration was normal. With the exception of the tracheal stoma and the aforementioned laryngeal, tracheal, and pharyngeal abnormalities, the results of a physical examination were normal.

After surgery was proposed, the patient was interviewed once by a psychiatrist and four times by members of the surgical team and a speech pathologist. All those involved agreed that the patient understood the risks and agreed that his motivation was appropriate. The procedure was approved by the institutional review board of the Cleveland Clinic Foundation, and the patient gave written informed consent.

A donor larynx was found after a six-month search. The donor, a 40-year-old man who had died from a ruptured cerebral aneurysm, had had no coexisting illnesses and had not smoked. Serologic tests for cytomegalovirus and Epstein–Barr virus were negative. HLA matching between the donor and the recipient was complete. The donor had been intubated for less than 48 hours before his death.

The entire pharyngolaryngeal complex, including six tracheal rings and the thyroid and parathyroid glands, was removed; most of the associated vasculature remained intact (Fig. 1). The left internal jugular vein was injured during removal, limiting subsequent anastomosis on the left side to the middle thyroid vein. The larynx was stored in University of Wisconsin solution and ice until implantation 10 hours later. The duration of ischemia was thus well within the acceptable 20-hour window.[5]

Surgical Procedure

Before surgery, the patient received cyclosporine, azathioprine, and methylprednisolone. During surgery, his laryngeal vasculature and innervation were delineated. The strap muscles, hyoid bone, and preepiglottic fat were removed from the donor's larynx, and perfusion was established before the recipient's larynx was removed (Fig. 1). We anastomosed the donor's right superior thyroid artery to that of the patient and the proximal end of the donor's right internal jugular vein to the end of the patient's relatively large common facial vein. The distal end of the donor's jugular vein was oversewn. Blood flow through the transplant — including the transplanted thyroid gland, the six tracheal rings, the larynx, and the pharynx — was seen within 30 minutes after clamp release.

We then performed a narrow-field laryngectomy and removed the portion of the patient's trachea above the upper half of the tracheal stoma. We split the patient's thyroid and repositioned the segments laterally. We left the patient's hyoid bone in place to ensure that the tongue base and laryngeal elevation were relatively normal. The pharynx had two midlevel strictures and one stricture at the esophageal inlet. Believing that a tight suture line would increase the risk of a fistula, we widened the patient's pharynx substantially by including in the transplant 75 percent of the donor's pharynx. We placed three permanent sutures, 1 cm apart, between the patient's hyoid bone and the donor's thyroid cartilage and then elevated and fixed the larynx to the hyoid bone (Fig. 1). The central suture incorporated the epiglottis to prevent prolapse.

Five tracheal rings were needed to reach the patient's tracheal stoma. The back of the tracheal wall was sutured to that of the donor, and the stoma was recreated superiorly. The left superior thyroid arteries were anastomosed in an end-to-end fashion. The left middle thyroid vein of the transplant was anastomosed in an end-to-side fashion to the patient's left internal jugular vein. Both

From the Departments of Otolaryngology (M.S., J.S., R.E., D.H., R.R.L., I.E.), Nephrology and Hypertension (W.B.), and Plastic and Reconstructive Surgery (R.Y.), Cleveland Clinic Foundation, Cleveland; and Lifelink Transplant Institute, Tampa, Fla. (J.M.). Address reprint requests to Dr. Strome at the Department of Otolaryngology, Cleveland Clinic Foundation, 9500 Euclid Ave., Cleveland, OH 44195.

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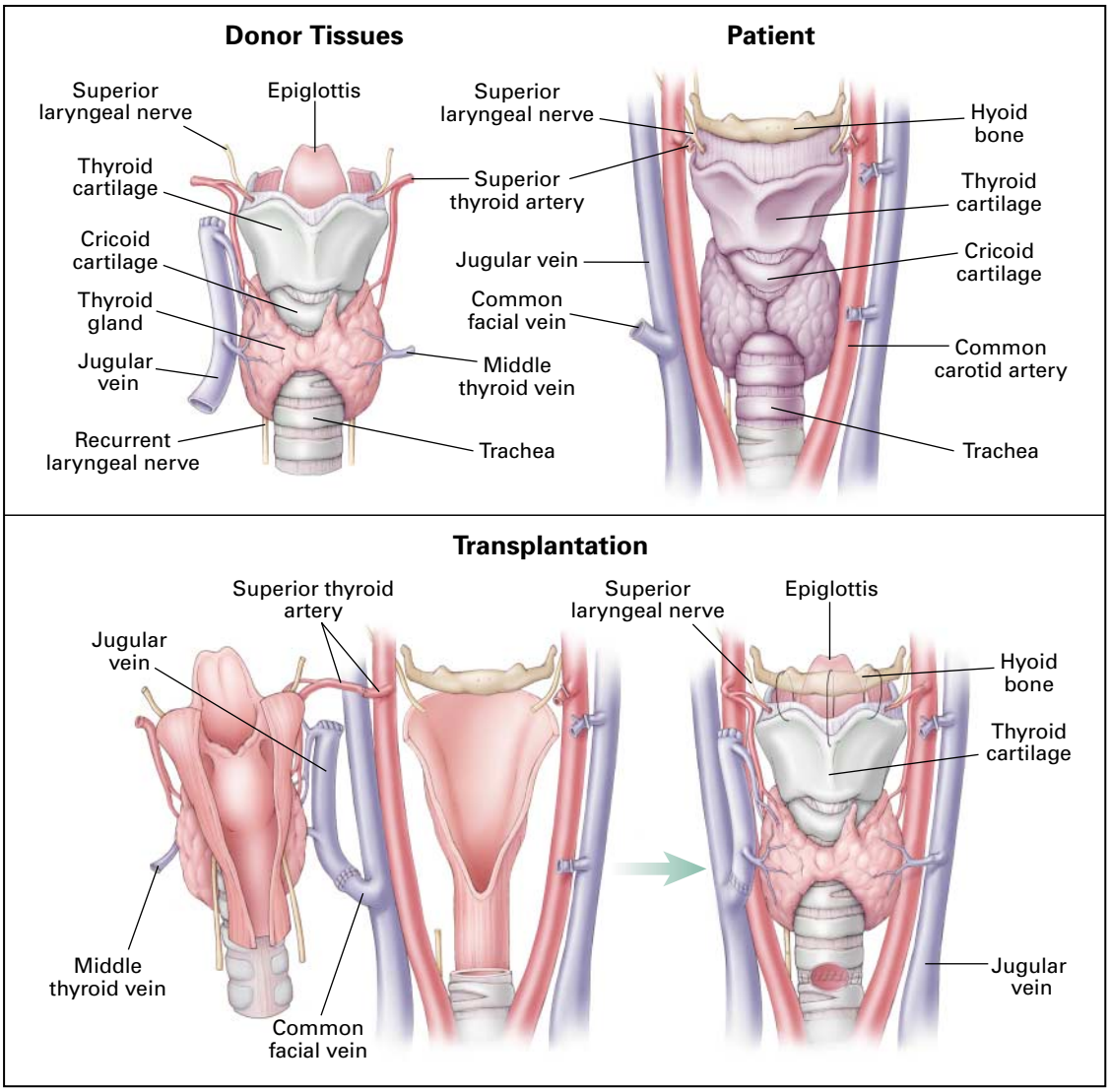

Figure 1. Transplantation of the Pharyngolaryngeal and Tracheal Complex.

The upper left panel shows the tissues obtained from the donor, including a portion of the trachea, the thyroid gland, the pharynx, the larynx, both superior laryngeal nerves, both superior thyroid arteries, both recurrent laryngeal nerves, a segment of the right jugular vein with contributions from the larynx and the pharynx, and the middle thyroid vein. The upper right panel shows the tissues removed from the patient (purple areas). The thyroid gland was split in the midline and retracted laterally. The lower left panel shows the pharynx and upper esophagus of the transplant split posteriorly in the midline, with the right superior thyroid artery anastomosed to that of the patient and the right jugular vein anastomosed to the patient's right common facial vein. The lower right panel shows the donor tissues after transplantation in the patient. The tracheal stoma is permanent and self-sustaining. Three circumferential sutures secure the thyroid cartilage to the hyoid bone, elevating the larynx. The midline suture also includes the epiglottis and pulls it anteriorly. Both superior thyroid arteries and superior laryngeal nerves are juxtaposed. The transplanted left middle thyroid is anastomosed in an end-to-side fashion to the patient's left jugular vein.

superior laryngeal nerves and the right recurrent laryngeal nerve of the transplant were sutured to those of the patient. The patient's left recurrent laryngeal nerve was not identified.

Postoperative Course

The tracheostomy tube and operative drains were removed the day after surgery. We prepared for the possibility of aspiration because all the motor and sensory nerves in the pharynx had been transected. Glycopyrrolate and atropine were administered to reduce salivary secretion. The patient was fed through a gastrostomy tube for 14 weeks, after which time he was able to swallow adequately. During the first week after surgery, he was given muromonab-CD3 (5 mg per day), cyclosporine (500 mg per day), methylprednisolone (50 mg per day, with the dose decreased to 20 mg per day by postoperative day 4), and mycophenolate mofetil (1 g twice daily).

Subsequently, the patient received cyclosporine, mycopheno-

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late mofetil, and prednisone in progressively decreasing doses, with his responses monitored by measurements of plasma drug concentrations and biopsies of the transplanted tracheal mucosa. None of the tracheal biopsy specimens revealed signs of rejection. At one month, the transplanted trachea was normal both on endoscopic examination and on microscopical examination of the biopsy specimens. Cyclosporine was given in doses needed to maintain trough plasma concentrations of 400 ng per milliliter. Six months after surgery, the patient's blood pressure and serum creatinine concentration had increased. Administration of additional antihypertensive drugs and a reduction in the dose of cyclosporine resulted in the resolution of these symptoms within six months.

The patient had one episode of rejection 15 months after transplantation. The quality of his voice declined over a period of several days until he became aphonic, at which time he sought treatment. His larynx was edematous. High doses of prednisone were administered, and his larynx returned to normal within three days. Tacrolimus was then substituted for cyclosporine, and he has had no further rejection episodes. He currently takes 7.5 mg of prednisone per day, 1 g of mycophenolate mofetil daily, and 4 mg of tacrolimus twice daily. His blood pressure and renal function are stable.

RESULTS

Voice Quality

On the third postoperative day, the patient uttered his first laryngeal speech in 20 years (the word "hello"). At one month, both vocal folds were lateral, creating a voice that was breathy with vibration generated by the aryepiglottic folds. At four months the right vocal fold was midline, and at six months the left vocal fold was just adjacent to the midline. We believe that the left recurrent laryngeal nerve of the transplant was reinnervated by the patient's small regional motor nerves. Electromyography confirmed that both vocal folds and the cricothyroid muscles had been reinnervated.

Subjective and objective measures of phonation improved steadily and became stable at normal or near-normal levels 16 months after transplantation. These measures included pitch, jitter (vocal quality), intensity (loudness), maximal phonation time, respiratory volume, and airflow (a measure of the efficiency of phonation). At 16 months, the pitch of the patient's voice changed, increasing its natural quality, as confirmed by a trained listener. At 36 months, the characteristics of his speech were all within the normal range. His voice sounded normal, and it served all his verbal communication needs. He was very pleased with the results and reported that his quality of life had improved "immeasurably." Unemployed before the transplantation, he has since become a motivational speaker.

Respiration and Swallowing

We initially planned to close the tracheal stoma one year after laser cordotomy of the left vocal fold. Closure would leave a serviceable airway without markedly affecting voice quality. The procedure is currently being actively considered. Attempts to provide a self-closing external valve at the site of the tracheal stoma were not successful. At 40 months, the stoma was self-sustaining, and it has not become crusted or granulated during 34 months of follow-up. Stimulation of the right side of the upper trachea through the stoma with a flexible laryngoscope elicited a sensation of touch but no cough, whereas there was no response on the left side.

Three months after transplantation, the supraglottis and vocal folds were sensitive to touch, which initiated a severe cough. Purposeful swallowing returned soon thereafter, and full oral alimentation was possible. A barium swallow revealed no aspiration of solids or liquids. The patient's sense of taste and smell returned.

Infection

The patient had a mild case of oropharyngeal thrush three weeks after transplantation, which subsided with decreasing doses of atropine and oral nystatin. He subsequently had three episodes of tracheobronchitis, at 16 and 18 weeks and at 15 months, that were successfully treated with oral amoxicillin clavulanate. Examinations with a fiberoptic laryngoscope through the stoma during each episode of tracheobronchitis suggested that infection, rather than aspiration, was the cause. During the first episode, the patient inexplicably stopped taking the trimethoprim–sulfamethoxazole given routinely after transplantation and had *Pneumocystis carinii* pneumonia, which cleared rapidly with intravenous antibiotic therapy.

Thyroid Effects

We also transplanted the donor's thyroid and parathyroid glands. The patient's serum calcium, phosphate, and thyroid hormone concentrations remained normal. Four months after transplantation, the four-hour uptake of iodine-123 by the thyroid was 5 percent (normal range, 5 to 15 percent). Imaging revealed that 83 percent of the activity was in the transplanted thyroid lobes and that 17 percent was in the patient's thyroid lobes. It is unlikely that the donor's parathyroid glands were functional after a 10-hour period of ischemia. Therefore, we think that the patient's own parathyroid glands were functioning normally.

DISCUSSION

This patient underwent transplantation of the larynx, trachea, pharynx, and thyroid and parathyroid glands, and the transplant has remained viable for 40 months. He has a human-sounding voice with inflection, range, and qualities unique to him, and he can swallow normally. Transplanting 75 percent of the donor pharynx did not compromise swallowing. Thus, when transplantation is a reconstructive procedure, a constricted pharynx can be widened without impairing swallowing, as long as sensation is restored.

The results in this patient show that laryngeal transplantation is feasible. We propose that potential candidates for transplantation include aphonic patients with laryngeal trauma, patients with large benign

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chondromas requiring laryngectomy, and patients who have undergone laryngectomy for cancer and who remain disease-free after five years.

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