INTRODUCTION

Long-segment tracheal defects are associated with significant morbidity and mortality. While airway defects <6cm in length may be reconstructed using primary re-anastomosis, defects >6 cm in length continue to challenge surgeons worldwide. It has been scientific dogma for half a century that single-staged tracheal transplantation was not possible because of the inability to restore blood flow to the transplanted organ. In lieu of single-staged transplantation, a variety of inventive staged reconstructive techniques has been employed to manage extensive airway defects. Temporary palliative stents have also been employed but these techniques are fraught with complications primarily due to the lack of ciliated epithelium required for a functional airway in a long-segment defect. Previously, no single-staged technique has emerged to manage these defects and achieved a truly functional construct.

We propose that successful long-segment tracheal reconstruction requires a rigid structure that maintains patency under dynamic conditions, a structure that will biologically integrate, and a structure with functional ciliated epithelium. A rigid structure is necessary to withstand the inspiratory pressures. A structure that fails to biologically integrate such as an alloplastic material, erode, become infected, and may invade into surrounding structures. Functional

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BRIEF COMMUNICATION

Single-stage long-segment tracheal transplantation

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Tracheal transplantation has been envisioned as a viable option for reconstruction of long-segment tracheal defects. We report the first human single-stage long-segment tracheal transplantation. Narrow-band imaging and bronchoscopic biopsies demonstrate allograft vascularization and viable epithelial lining. The recipient was immunosuppressed with Tacrolimus, Mycophenolate mofetil, and corticosteroids. Six months after transplantation, the trachea is both functional and the patient is breathing without the need of a tracheostomy or stent.

KEYWORDS
clinical research/practice, organ procurement, surgical technique, vascularized composite and reconstructive transplantation

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We propose that successful long-segment tracheal reconstruction requires a rigid structure that maintains patency under dynamic conditions, a structure that will biologically integrate, and a structure with functional ciliated epithelium. A rigid structure is necessary to withstand the inspiratory pressures. A structure that fails to biologically integrate such as an alloplastic material, erode, become infected, and may invade into surrounding structures. Functional
Mucociliary clearance is a critical to airway hygiene to prevent life-threatening mucous plugging. To this end, tracheal transplantation has been proposed as a solution, as other techniques have proved inadequate. The scientific dogma perpetuated for more than half a century that the segmental blood supply of the tracheoesophageal complex is too small to enable microvascular transplantation has stymied investigation aimed at single-stage tracheal transplantation. This report details the first successful single-stage human vascularized long-segment tracheal transplantation.

The planning for this novel procedure included formal tracheal vascular composite allograft approval from the United Network for Organ Sharing (UNOS) as well as institutional review board (IRB) approval (STUDY-15-00825). All human participants gave written informed consent.

2 MATERIALS AND METHODS

2.1 The patient and the donor

The patient is a 56-year-old female social worker who was emergently intubated for a severe asthma attack 7 years ago. As a result of the prolonged intubation and subsequent tracheostomy, the patient developed long-segment cricotracheal stenosis (8 cm in length) with complete cricoid stenosis and remained dependent on an extended length tracheostomy. The patient’s airway was severely compromised by stenosis and tracheomalacia. The lumen was severely damaged by the prior placement of airway stents and an extended length tracheostomy tube (Figure 1). The patient underwent six failed attempts at conventional tracheal reconstruction including a failed end-to-end anastomosis and cartilage grafts. The patient became aware of the human tracheal transplantation program at Mount Sinai and requested participation. The patient’s medical history includes hypertension, asthma, and sarcoidosis. After extensive consultation related to the risks of undergoing a novel procedure the patient elected to undergo tracheal transplantation. She completed a full psychosocial and transplant evaluation and was counseled periodically while she awaited transplantation. The recipient was wait listed for 8 months while a suitable donor was identified. We preferred to identify a male donor to permit evaluation of donor allograft re-epithelialization. In choosing a donor, it was also essential that the donor had not been subject to prior neck surgery, had not form of thyroid disease, and did not have a central venous line placed in the internal jugular vein.

The donor was a 37-year-old male with a past medical history of end-stage renal disease who underwent renal transplantation 2 years previously and was admitted to an outside hospital after having an acute, non-traumatic subarachnoid hemorrhage resulting in severe brain injury. He was declared brain dead in the intensive care unit at the outside institution and his family was counseled and consented for donor procurement. To assess the patient’s suitability for tracheal organ procurement, the patient underwent a thyroid ultrasound to rule out thyroid malignancy and evaluation of the neck for central venous access or tracheostomy that may preclude organ procurement. Once evaluated and consented, the donor was transferred to The Mount Sinai Hospital for organ procurement and tracheal donation.

2.2 Preoperative immunological work up and immunosuppression

In preparation for transplantation, the recipient underwent complement-dependent cytotoxicity (CDC) and flow cytometry cross matches with negative results. There was no evidence of donor-specific antibodies. Immunosuppression included induction with anti-thymocyte globulin (6 mg/kg; the patient’s weight was 71 kg at the time of transplantation) and then tacrolimus, mycophenolate mofetil and a corticosteroid taper. Triple immunosuppressive therapy was initiated as follows:

Tacrolimus initiated immediately following transplantation with dose adjustments to achieve target trough ranges as follows:
a. 10–12 ng/ml during months 0–3  
b. 8–10 ng/ml during months 3–6  
c. 6–8 ng/ml during months 6–12  
d. 4–6 ng/ml after month 12

Mycophenolate Mofetil initiated immediately after transplantation as follows:

a. 1 g BID during months 0–6  
b. 500 mg BID after month 6

Steroids were initiated as follows:

a. Methylprednisolone 500 mg pre-transplant  
b. Methylprednisolone 250 mg POD #1  
c. Methylprednisolone 125 mg POD #2  
d. Methylprednisolone 60 mg POD #3  
e. Prednisone – standard steroid taper beginning on POD #4

### 2.3 Operative technique

The procurement and the transplant were performed at Mount Sinai Hospital in side by side operating rooms to facilitate transport or the donor organ and limit ischemic time.

#### 2.3.1 Donor procurement

The tracheal procurement entailed dissecting the internal jugular vein and carotid artery from the clavicle to the terminal superior branches. Bilaterally, the superior thyroid arteries and veins were dissected to the superior thyroid poles. Bilaterally, the superior thyroid poles were dissected free of the larynx. The cricoid cartilage and the trachea were separated from the posterior attachments of the prevertebral fascia maintaining the tracheoesophageal complex. The donor thyroid gland and infrahyoid muscles were procured with the trachea. Bilaterally, the thyrocervical trunk and the inferior thyroid arteries were dissected and isolated. The posterior attachments of the tracheoesophageal complex were dissected free from the prevertebral fascia. A median sternotomy was then performed to expose the aortic arch. The surgical team placed vessel loops around all of the superior arterial vessels including the internal carotid arteries and the superior branches of the internal jugular veins bilaterally. The allograft was prepared for procurement. The transplant team simultaneously prepared the abdomen for the liver procurement and aortic cannulation.

#### 2.3.2 Recipient preparation

The recipient was prepared through a low apron neck incision followed by dissection of the carotid artery and arterial branches as well as the transverse cervical arteries. The internal jugular venous system as well as the transverse cervical veins were prepared for the venous microvascular anastomosis. The internal jugular venous system as well as the transverse cervical veins were prepared for the venous microvascular anastomosis.

The distal trachea was dissected inferiorly and released from the mediastinal attachments. At 2 cm above the carina, the trachea was transected and an endotracheal tube was placed and secured. The superior tracheal dissection revealed extensive scarring of the tracheal lumen as well as a near-complete cricoid stenosis extending just inferior to the vocal folds. The tracheal dissection revealed extensive tracheal lumen scarring and complete cricoid stenosis. All but the posterior third of the cricoid cartilage was resected in order to address the stenosis and maintain laryngeal innervation. The length of the long-segment tracheal defect from the inferior thyroid cartilage to the distal transected trachea was 9 cm.

#### 2.3.3 Cross-clamping and perfusion

Prior to cross-clamping, the inferior donor trachea, below the level of the carina, was incised and there was brisk bleeding demonstrating perfusion of the trachea to the distal carina. Cross-clamping and perfusion with University of Wisconsin solution was initiated through the aortic arch and drained though incisions in the inferior internal jugular veins. There was complete perfusion through the thyro-tracheal graft. Once the perfusion had been completed, the arterial branches including the thyrocervical trunk, internal jugular vein, and carotid arteries were transected. The esophagus and pharynx were transected and stapled to prevent soilage and the graft was removed from the donor and brought to the adjoining recipient room. The total time from donor cross-clamping to graft procurement was 26 min (Figure 2A).

Each of the allograft vessels was prepared for microvascular anastomosis on a side table with the microscope. The donor cricoid was included in the graft segment; the length of the graft segment was 11.5 cm extending from the cricoid cartilage to the bisection of the carina. The esophagus was vertically split in the midline and the lumen mucosa was dissected from the graft. The esophageal muscularis and the vascular anastomotic network between the inferior thyroid artery, esophageal musculature, and the trachea, were left intact.

#### 2.3.4 Tracheal implantation

The allograft was placed into the recipient bed and the patient was ventilated through the inferior tracheal stoma. The inferior posterior and superior posterior membranous trachea were reconstructed using 3-0 absorbable suture. Once the allograft was secured with posterior wall sutures, the microscope was used to perform the microvascular anastomoses (Figure 2B).
The allograft was reperfused once the allograft left lingual artery to the recipient left facial artery and the allograft left internal jugular vein end to side anastomosis with the recipient left internal jugular vein was complete; effectively ending the warm ischemic time, which was seventy-six minutes. The cold ischemic time was 78 min. After reinitiating vascular flow, there was brisk perfusion of the distal tracheal cartilage and membranous portions of the trachea to the level of the carina. The remaining vascular anastomoses were completed and the inferior tracheal defect was closed with a series of interrupted 2.0 antibiotic-impregnated poliglecaprone sutures. The superior tracheal anastomosis was left open to accommodate the endotracheal tube and serve as a port for postoperative bronchoscopy and monitoring.

2.4 | Postoperative course

Postoperatively, the patient was treated with triple immunosuppression with Tacrolimus, Mycophenolate mofetil, and corticosteroids. The patient remained intubated after the procedure and was extubated on post-operative day 6. The graft was monitored with twice daily endoscopy and narrow band imaging. Endoscopy performed daily demonstrated well-perfused confluent mucosa. Narrow band imaging (inset) demonstrated vascularization of the submucosal allograft. There is an even distribution of the vascular plexus without evidence of ischemia.
daily bedside trans-stomal bronchoscopy with narrow-band imaging (NBI). Postoperatively, the tracheal mucosa was consistently pink and healthy appearing and NBI demonstrated excellent mucosal vascular perfusion (Figure 3). Tracheal biopsies were taken on postoperative days 9, 16, and 30, 42, 72, and 86 for analysis. Biopsies were processed for electron microscopy (EM) and hematoxylin and eosin (H&E) (Figure 4A–C). On postoperative day 13, the patient began an oral diet. Daily tracheal bronchoscopy consistently demonstrated pink, well-vascularized mucosa consistent with a healthy and well-perfused allograft.

3 | DISCUSSION

Advancements and innovations in transplant science have set the stage to expand human vascularized composite allografts to address complex reconstructive dilemmas that cannot be managed with traditional reconstructive techniques.9,10 Extensive tracheal defects may result from traumatic intubation, congenital birth defects, burn/injury, ingestion injuries, severe infections or neoplasms of the trachea or adjacent structures. Defects >6 cm represent a significant reconstructive challenge. The scientific dogma based on historical observations dating back more than half a century suggested that tracheal transplantation was not possible because there was no axial vascular supply to the trachea that would lend itself to microvascular revascularization. The perpetuation of this dogma has led to a variety of creative procedures in lieu of transplantation to manage extensive tracheal defects.9,10 Tracheal revascularization is not only critical for cartilage vascularity and tracheal anastomotic healing but also provides blood supply to the most critical element of airway reconstruction, the ciliated tracheal mucosa. The ciliated mucosa characteristic of the tracheal lumen provides pulmonary hygiene by transporting inhaled particulate matter from the lungs to the oral cavity, where they can be expectorated or swallowed. The critical role of mucociliary transport is highlighted by conditions such as immotile cilia syndrome, an autosomal recessive disease characterized by abnormal ciliary motion and impaired mucociliary clearance. This disorder leads to recurrent or persistent respiratory infections as a result of mucous plugging. Similarly, tracheal reconstructive options which do not include functional ciliated mucosa, such as autografts or manufactured tracheal stents, do not re-establish mucociliary clearance and often lead to life-threatening airway mucous plugging and pneumonia.

In spite of the longstanding dogma that the trachea is not amenable to revascularization, research has demonstrated that in the canine model, the superior thyroid artery and vein provide adequate vascular supply for the transfer of long-segment tracheal autografts and allografts.11,12 Subsequent work in humans by our group during in a series of dye perfusion studies at the time of donor procurement without the intent to transplant, have demonstrated that the superior thyroid vessels and the inferior thyroid artery provide robust perfusion of the trachea from the cricoid to the carina. These dye perfusions depict an important anatomical relationship first illustrated by French anatomist Jean-Baptiste Marc Bourgery in the early 19th century and later illustrated by Furlow and Mathisen.13,14 Notably, the inferior thyroid artery gives off a tracheoesophageal branch that supplies the esophagus and contributes segmental blood supply to the trachea. Therefore, preservation of the tracheoesophageal complex and its associated vascular network seems critical in preserving the tracheal blood flow (Figure 5).

There have been prior successful reports of laryngeal transplants revascularized using the superior thyroid artery and vein that have included short segments of trachea with the laryngeal allograft.15,16 However, tracheal allografts represent a distinct revascularization challenge. We believe that blood flow to the tracheal allograft relies on distinct arterial and venous connections included in the esophageal musculature. This vascular network, supplied by the inferior thyroid artery, may be important to ensuring adequate blood supply and drainage to the distal-most aspect of the long-segment tracheal graft and potentially a tracheo-esophageal composite allograft.

**FIGURE 4** Histology. Histology was performed on biopsied on postoperative days 6, 9, 30, 42, and 72. (A) An endobronchial biopsy obtained 6 days after transplantation shows predominantly squamous metaplastic epithelium with patchy neutrophilic infiltrates in the superficial aspects and on the surface. Mild lymphocytic infiltrates are present in the submucosa. Detached strips of ciliated epithelium are indicated by the arrow. Hematoxylin and Eosin (H&E 200x). (B) An endobronchial biopsy obtained on postoperative day 30 shows reappearance of ciliated epithelium. Chronic inflammation is present but the acute inflammation seen in the first biopsy has resolved. (H&E 400x). (C) Electron microscopy demonstrates morphologically normal cilia.
Long-segment tracheal reconstruction requires a rigid structure able to tolerate negative inspiratory pressures, a structure that will biologically integrate, and a structure with functional mucocilia. Biological integration is critical to prevent infection, rejection, and extrusion; mucociliary function provides essential pulmonary hygiene. The failure to reestablish mucociliary transport results in stasis of secretions and life-threatening airway obstruction. Tracheal transplantation is the only reconstructive option that accomplishes these objectives.

Rodent and canine transplantation models demonstrate that immediately following tracheal transplantation, the ischemic-sensitive ciliated columnar epithelium partially sloughs and donor and recipient basal cells repopulate the graft reestablishing functional ciliated epithelium. Post-transplant biopsies in this patient demonstrate a similar pattern of mucosal sloughing followed by basal cell differentiation and cilia repopulation. Immediately following transplantation, we found the graft segment required suctioning to maintain a clean and patent airway. Through the course of healing, the graft segment required less suctioning and by day twenty, the graft maintained a clean and patent airway requiring no suctioning. This suggests that mucociliary function resumed. This was supported by the EM sections demonstrating progressive repopulation of ciliated epithelium.

Cytogenomics performed on biopsies from the distal third of the allograft on day thirty demonstrated progressive re-epithelialization with recipient mucosa. On day 86, the recipient epithelium within the donor graft increased to 75.3% meeting the criteria for chimerism; a phenomenon that was observed in experimental allografts (Figure 6). At the time of this submission, we are performing twice monthly transtracheal endoscopy in the clinic. We are scheduled to close the small stomal port that has been used to provide access the allograft for bronchoscopy and biopsies to follow the evolution of the graft and monitor for rejection. In the future, we will perform trans-nasal bronchoscopy and biopsies in the clinic setting.

The population of patients that may benefit from tracheal transplantation include patients with life-threatening circumferential long-segment airway disease. As we have a better understanding of the limitations of tracheal transplantation, this procedure may be extended to patients with extensive cervical trachea defects, trachea-esophageal fistula patients, and potentially those with congenital tracheo-esophageal disease. The future application of this procedure must be carefully considered because in the event of graft loss, while a cervical defect may be managed with an extended length tracheostomy, a thoracic defect may not be compatible with life.

Furthermore, we are monitoring the patient for anastomotic stenosis. While this has not yet occurred, it represents a dilemma for lung transplantation patients. In the event of stenosis, dilation may be appropriate. The future management of this patient will include careful assessment for chronic rejection which, if encountered, will be managed with immunosuppressive boosts. Unlike other vascularized tissue allografts, namely face and hand transplantation where rejection episodes are high, we have not yet witnessed an acute rejection. Finally, in preparation for this procedure, we performed a series of procurements without the intent to transplant. During these procurements, concomitant liver and kidney procurements were performed. While tracheal procurement is easily manageable during a concomitant kidney and/or liver procurement, this may not be possible during a heart or lung procurement. This does not currently represent a conflict because of the rarity of tracheal transplantation, this may need to be addressed if tracheal transplantation becomes more common.
4 | CONCLUSION

This report documents the first-in-human single-stage vascularized human tracheal transplantation. Revascularization was achieved with a novel vascular supply construct and the recipient was successfully immunosuppressed with a triple immunosuppression. This report demonstrates that tracheal revascularization and human transplantation is possible; and this approach may provide a new field of research and techniques for the reconstruction of patients with extensive and life-threatening airway defects.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

AUTHOR CONTRIBUTIONS

Eric M. Genden, MD, MHA contributed to conceptualization, methodology, project administration, supervision, and writing. Brett A. Miles, DDS MD contributed to methodology, project administration, supervision, and writing. Timothy J. Harkin, MD; Samuel DeMaria, MD; Andrew J. Kaufman, MD; and Sander S. Florman, MD contributed to methodology, project administration, and supervision. Erica Mayland, MD and Vivian Kaul, MD contributed to methodology, project administration, and writing. All authors have verified the underlying data.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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