

Feasibility of Bioengineered Tracheal and Bronchial Reconstruction Using Stented Aortic Matrices

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IMPORTANCE Airway transplantation could be an option for patients with proximal lung tumor or with end-stage tracheobronchial disease. New methods for airway transplantation remain highly controversial.

OBJECTIVE To establish the feasibility of airway bioengineering using a technique based on the implantation of stented aortic matrices.

DESIGN, SETTING, AND PARTICIPANTS Uncontrolled single-center cohort study including 20 patients with end-stage tracheal lesions or with proximal lung tumors requiring a pneumonectomy. The study was conducted in Paris, France, from October 2009 through February 2017; final follow-up for all patients occurred on November 2, 2017.

EXPOSURES Radical resection of the lesions was performed using standard surgical techniques. After resection, airway reconstruction was performed using a human cryopreserved (-80°C) aortic allograft, which was not matched by the ABO and leukocyte antigen systems. To prevent airway collapse, a custom-made stent was inserted into the allograft. In patients with proximal lung tumors, the lung-sparing intervention of bronchial transplantation was used.

MAIN OUTCOMES AND MEASURES The primary outcome was 90-day mortality. The secondary outcome was 90-day morbidity.

RESULTS Twenty patients were included in the study (mean age, 54.9 years; age range, 24-79 years; 13 men [65%]). Thirteen patients underwent tracheal ($n = 5$), bronchial ($n = 7$), or carinal ($n = 1$) transplantation. Airway transplantation was not performed in 7 patients for the following reasons: medical contraindication ($n = 1$), unavoidable pneumonectomy ($n = 1$), exploratory thoracotomy only ($n = 2$), and a lobectomy or bilobectomy was possible ($n = 3$). Among the 20 patients initially included, the overall 90-day mortality rate was 5% (1 patient underwent a carinal transplantation and died). No mortality at 90 days was observed among patients who underwent tracheal or bronchial reconstruction. Among the 13 patients who underwent airway transplantation, major 90-day morbidity events occurred in 4 (30.8%) and included laryngeal edema, acute lung edema, acute respiratory distress syndrome, and atrial fibrillation. There was no adverse event directly related to the surgical technique. Stent removal was performed at a postoperative mean of 18.2 months. At a median follow-up of 3 years 11 months, 10 of the 13 patients (76.9%) were alive. Of these 10 patients, 8 (80%) breathed normally through newly formed airways after stent removal. Regeneration of epithelium and de novo generation of cartilage were observed within aortic matrices from recipient cells.

CONCLUSIONS AND RELEVANCE In this uncontrolled study, airway bioengineering using stented aortic matrices demonstrated feasibility for complex tracheal and bronchial reconstruction. Further research is needed to assess efficacy and safety.

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Over the last decade, new procedures in the field of airway transplantation have gained attention primarily through case reports or small studies.¹⁻⁶ Due to the lack of prospective data, these interventions have failed to achieve standard of care status. An efficient airway replacement could potentially benefit many patients with lung cancer and eliminate the need for high-risk thoracic surgical procedures including pneumonectomies. Airway replacement also could be an option for patients with end-stage tracheobronchial disease for whom palliative treatment is often proposed.

In 1997, a research program on airway transplantation using stented aortic matrices was initiated in the laboratory of the Alain Carpentier Foundation. A series of 7 preclinical animal studies using a sheep model showed that autologous and fresh or cryopreserved allogeneic aortic grafts could be valuable airway substitutes.⁷ The regeneration of epithelium and de novo generation of cartilage were observed within the aortic matrices, thus allowing stent removal after only 6 months. Although controversial, the hypothesis that bone marrow mesenchymal stem cells play a role in this process of in vivo tissue engineering has been proposed.⁸ These favorable results led to the first human applications in patients with extensive tracheal diseases or complex tumors that would otherwise necessitate pneumonectomies.⁹⁻¹²

De novo generation of cartilage within cryopreserved aortic allografts has been observed recently.¹² This process originated from the recipient cells, which was observed in animal models. Moreover, remaining viable matrix cells have been identified to play a critical role in the regenerative process as a way to release proangiogenic, chemoattractant, proinflammatory or proimmunomodulatory cytokines, and growth factors. This prospective study was designed to evaluate the feasibility of airway bioengineering using stented cryopreserved aortic allografts as biological matrices.

Methods

Study Design

The study was sponsored by Direction de la Recherche Clinique at Assistance Publique-Hôpitaux de Paris, which is a consortium of university hospitals in Paris, France. The protocol was written by 2 of the principal investigators (E.M. and E.V.), it was approved by the French national institutional ethical review board on March 14, 2011, and it appears in **Supplement 1**. The initial protocol focused on bronchial transplantation to avoid a pneumonectomy in patients with extensive lung cancer.

To extend the study to all types of major (malignant or benign) lesions of the trachea and bronchi requiring airway transplantation, 3 amendments to the protocol were approved by the institutional ethical review board on March 27, 2012, October 25, 2012, and June 5, 2013. Before approval of the study and its amendments, 4 procedures had been accepted by the ethical review board. An independent data and safety monitoring board periodically reviewed the study outcomes. Written informed consent was obtained from all patients.

Key Points

Question Is airway bioengineering using stented aortic matrices for complex tracheal and bronchial reconstruction feasible in humans?

Findings In this uncontrolled cohort study that included 20 patients, 13 were able to undergo tracheal, bronchial, or carinal transplantation. The overall 90-day mortality rate was 5%.

Meaning This preliminary study suggests feasibility of human airway bioengineering using stented aortic matrices for tracheal and bronchial reconstruction.

Patients

Eligible patients underwent a standard preoperative evaluation and cardiopulmonary tests. A multidisciplinary team approved the inclusion and exclusion criteria. Patients were included in the study if they (1) had proximal lung tumors requiring a surgical resection (pneumonectomy, carinal resection, or sleeve lobectomy) that may or may not have been treated with neoadjuvant chemotherapy and had adequate or compromised preoperative lung function tests; or (2) had significant major malignant or benign lesions of the trachea and bronchi untreated with conventional therapeutic approaches.

Patients were excluded from the study if they (1) were younger than 18 years; (2) were unable to give consent or not affiliated with the French Social Security System; (3) had a lung tumor requiring a standard lobectomy; (4) had nonresectable major locally invasive tumors; (5) had contralateral lymph node invasion; (6) had metastatic disease with the exception of a unique resectable brain metastasis; (7) had tracheal lesions requiring standard resection with direct anastomosis; (8) had an iodine allergy; or (9) received a preoperative evaluation indicating an inability to undergo a standard lobectomy.

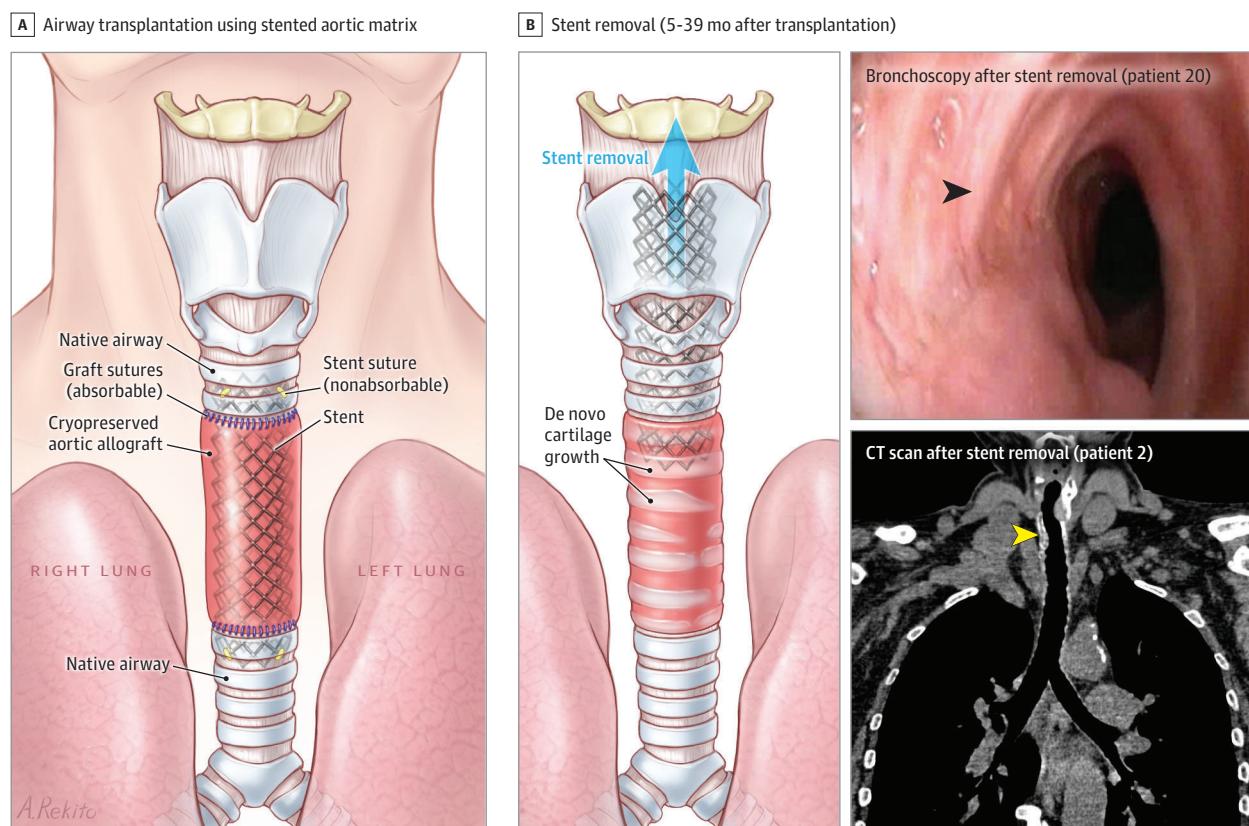
Treatment

After enrollment in the study, patients underwent an intensive preoperative respiratory conditioning program. The human cryopreserved (-80°C) aortic allograft, which was not matched by the ABO and leukocyte antigen systems, was ordered from a certified tissue bank (Saint-Antoine, Etablissement Français du Sang, Assistance Publique-Hôpitaux de Paris). To prevent airway collapse, a custom-made, fully covered conical nitinol stent (Silmet, Novatech) or a silicone stent (Tracheobronxane Dumon, Novatech) were manufactured according to preoperative measurements obtained via computed tomography.

The first step was to evaluate whether a complete surgical resection with adequate margins was needed. The second step was to determine whether a conventional approach should be taken using direct end-to-end anastomosis for tracheal lesions or a lobectomy or bilobectomy for lung tumors. The third step was to determine whether an airway transplantation was needed.

Radical resection of the lesions was performed using standard surgical techniques. A conventional solution for airway

Figure 1. De Novo Generation of Cartilage Within Stented Cryopreserved Aortic Matrices After Surgical Resection of End-Stage Tracheal Lesions or Proximal Lung Tumors



A, Schematic view of airway transplantation using a stented aortic matrix. After resection with adequate surgical margins of end-stage tracheal lesions or proximal lung tumors, the native airway was reconstructed using a cryopreserved aortic allograft. This biological matrix was supported by a stent to prevent airway collapse. The native airway and the aortic graft were anastomosed with continuous absorbable sutures. Both ends of the stent were fixed to the native airway using 4 nonabsorbable sutures (yellow stitches). **B**, Schematic view of stent removal after airway reconstruction and clinical follow-up. De novo generation of cartilage within the aortic matrix allowed removal of stents 5 to 39 months after transplantation. Top right, patient 20

had complete resection of recurrent thyroid carcinoma with tracheal invasion followed by tracheal transplantation using a cryopreserved aortic allograft. Bronchoscopy at 8 months after tracheal transplantation showed de novo generation of tracheal cartilage (black arrowhead) (Video). The patient was able to breathe and speak normally through newly formed airways at last follow-up after both stent removal at 5 months and tracheostomy tube decannulation at 7 months. Bottom right, patient 2 had end-stage postintubation stenosis that was treated with tracheal transplantation. Chest computed tomographic (CT) scan at last follow-up (7 years 1 month) after stent removal showed a newly formed trachea (yellow arrowhead).

reconstruction was preferred when feasible. If used, the cryopreserved aortic allografts were removed from the dry ice, then thawed in container bags for 10 minutes at room temperature, followed by 10 minutes in a water bath at 37°C. Next, the allografts were washed with a sterile saline solution for 5 minutes before implantation and were used for airway reconstruction, pulmonary artery reconstruction, or both.

At the end of the operations, the allografts were covered circumferentially with a local muscle flap to promote neovascularization and prevent fistulization. Sterno-omo-thyroid muscle flaps were used for tracheal reconstructions; pectoralis major muscle flaps were used for carinal reconstructions; and latissimus dorsi or intercostal muscle flaps were used for bronchial reconstructions. The techniques used followed guidelines established during human and other experimental studies.⁷⁻²⁰

In Figure 1, the final aspect of the airways after surgical resection and reconstruction is shown schematically. None

of the patients received immunosuppressive therapy per the usual recommendations when cryopreserved aortic allografts are used in vascular surgery. Low-molecular-weight heparin was administered for postoperative venous thromboembolism prophylaxis. Until stent removal, an aerosolized saline solution was administered 3 times daily to prevent airway obstruction.

Follow-up and Assessment of Outcomes

Patients were followed up for 90 days. The outcomes of mortality and morbidity were assessed, including complications directly related to the allograft, the stent, or both. Patients were systematically examined at 30, 60, and 90 days. There was a 7-day window around each time point during which patients could have been examined (eg, on day 23 or on day 37 for the 30-day time point). If required, complementary examinations were performed such as chest radiography, computed tomography, and bronchoscopy. The primary outcome was

90-day mortality. The secondary outcome was 90-day morbidity. After 90 days, all patients were followed up for long-term mortality and morbidity outcomes.

Biopsy specimens were obtained from cryopreserved aortic allografts after stent removal in a woman (patient 2) who received an allograft from a male donor at 15 months and in a man (patient 4) who received an allograft from a female donor at 39 months. Tissues identified as neoepithelium, neocartilage, and granuloma were isolated and used for histological studies. Biopsy specimens from patient 2 were used for engraftment (chimerism) studies. The biological study protocols are detailed in the eMethods in [Supplement 2](#).

For all patients, the last follow-up visit occurred on November 2, 2017. The following data were collected for each patient: sex, age, medical history, type of airway disease, tumor localization, preoperative treatment, indication for inclusion in the protocol, date of the procedure, type of operation, duration of hospitalization, 90-day mortality and morbidity, histopathological specimen examination, postoperative treatment, delayed complications (after 90 days), stent removal timing, and status at last follow-up visit.

Statistical Analysis

The predefined sample size was 20 patients. This sample size enables estimation of a 90-day survival rate with a maximal half-width of its 2-sided 95% CI equal to $\pm 17.5\%$. The reported results include assessments from all 20 patients. All analyses were made using SAS version 9.4 (SAS Institute Inc).

Results

Patients

From October 2009 through February 2017, 20 patients were included in the study. Eight patients (40%) were referred from other medical centers. There were 13 male and 7 female patients ranging in age from 24 to 79 years with a mean age of 54.9 years. The patient characteristics, types of preoperative treatments, and indications for inclusion appear in [Table 1](#).

Fourteen patients were included to avoid a pneumonectomy for non-small cell lung cancer ($n = 11$), carcinoid tumor ($n = 2$), or rhabdomyosarcoma ($n = 1$). Five patients had extensive benign ($n = 3$) or malignant ($n = 2$) tracheal lesions for which previous treatment had failed. One patient presented with a carcinoid tumor extending to the distal trachea, carina, and main right bronchus.

Procedures

The interventions performed for each patient are detailed in [Table 2](#) and [Figure 2](#). Thirteen patients underwent a tracheal ($n = 5$), carinal ($n = 1$), or bronchial ($n = 7$) transplantation using a stented cryopreserved aortic allograft. Two of the patients who underwent bronchial reconstruction also underwent a partial replacement of the pulmonary artery using the same allograft to avoid a pneumonectomy. Seven patients did not receive airway transplantation for the following reasons: medical contraindication appeared after enrollment ($n = 1$), unavoid-

able pneumonectomy ($n = 1$), exploratory thoracotomy only ($n = 2$), and a lobectomy or bilobectomy was possible ($n = 3$).

Primary Outcome

The details regarding the primary outcome for each patient appear in [Table 2](#). Among all 20 patients, the 90-day mortality rate was 5% (1 patient underwent a carinal transplantation and died). Among the 13 patients who underwent airway transplantation, the 90-day mortality rate was 7.7% ($n = 1$). The 90-day mortality rate was 0% for the patients who had a tracheal ($n = 5$) or bronchial transplantation ($n = 7$).

Secondary Outcomes

The details regarding the secondary outcomes for each patient appear in [Table 2](#). The mean length of hospitalization was 10.5 days and ranged from 6 to 22 days. Among the 13 patients who underwent airway transplantation, major 90-day morbidity events occurred in 4 (30.8%) and included laryngeal edema, acute lung edema, acute respiratory distress syndrome, and atrial fibrillation. There was no adverse event directly related to the surgical technique. All general complications resolved except for a massive cerebrovascular accident, resulting in the death of the patient.

Long-term Follow-up

Long-term follow-up did not identify any major complications specifically related to the allograft or the stent ([Table 3](#)). Minor stent-related complications (tracheal or bronchial granulomas) were found in 7 patients and required treatment management with bronchoscopy. A temporary tracheostomy, via the stented allograft, was required due to severe laryngeal edema in patient 2. Extensive granulomas required early stent removal in patient 20 at 5 months and a temporary tracheostomy from months 5 to 7 until the allograft was structurally strong enough.

Stent removal was possible in the majority of patients ($n = 9$; 69.2%). It was performed postoperatively between months 5 and 39 at a mean of 18.2 months. At a median follow-up of 3 years 11 months (maximal follow-up of 7 years 1 month), 10 patients (76.9%) were alive. Of these 10 patients, 8 (80%) breathed normally through newly formed airways after stent removal ([Video](#)). As of November 2, 2017, the stent was still in place in patients 3 and 17.

In biological studies, the explant cell culture demonstrated that the cells contained within the cryopreserved aortic allografts were viable and able to proliferate after thawing. The absence of SRY donor DNA 15 months after surgery in biopsy specimens from patient 2 suggested a progressive disappearance of donor cells from the cryopreserved aortic allograft in parallel to its colonization by the host's cells. Pathological examination of superficial allograft biopsies showed the regeneration of mixed respiratory epithelium ([Figure 3A](#)).

The positive labeling of a biopsy sample from the cryopreserved aortic allograft at 39-month implantation for specific cartilage markers (type 2 collagen and Sox9) suggested the presence of cartilage-like cells ([Figure 3B, C](#)). Nonimplanted cryopreserved aortic allografts were negative for these markers.

Table 1. Patient Characteristics, Preoperative Treatment, and Indication for Inclusion in the Study

Patient No.	Sex	Age, y	Medical History	Type of Airway Disease	Description of Localization	Type of Preoperative Treatment	Indication for Study Inclusion
1	M	78	Prostatic adenoma, past smoker (50 pack-years), and COPD	Non-small cell lung cancer, large cell subtype	Right lung and extending to main bronchus and left atrium	Neoadjuvant chemotherapy (3 cycles)	To avoid pneumonectomy
2	F	58	Thyroidectomy for hyperthyroidism and idiopathic laryngeal edema	Postintubation benign tracheal stenosis and upper airway malacia	Laryngotracheal	Conventional endoscopic and surgical treatment	Extensive lesion and failure of previous treatment
3	F	24	Toll-like receptor deficiency and fulminant hepatitis (HSV type 2)	Postintubation benign tracheal stenosis	Laryngotracheal	Conventional endoscopic and surgical treatment	Extensive lesion and failure of previous treatment
4	M	33	Severe epilepsy and tracheal intubation in ICU	Postintubation benign tracheal stenosis	Laryngotracheal	Conventional endoscopic and surgical treatment	Extensive lesion and failure of previous treatment
5	M	59	Alcoholic cirrhosis, obesity, past smoker (80 pack-years), and COPD	Non-small cell lung cancer, squamous cell subtype	Right lung and extending to proximal bronchi and pulmonary artery	Neoadjuvant chemotherapy (3 cycles)	To avoid pneumonectomy
6	F	41	Obesity (BMI of 37.5 ^a) and gestational diabetes	Extended carcinoid tumor for >3 y	Lower trachea, carina, right lung, and mediastinal nodes	Palliative endoscopic treatment	Not accessible to conventional surgery
7	M	62	Coronary stenting, past smoker (40 pack-years), and COPD	Non-small cell lung cancer, squamous cell subtype	Left lung, upper lobe extending to main bronchus	Neoadjuvant chemotherapy (3 cycles)	To avoid pneumonectomy
8	M	57	Carotid surgery, past smoker (70 pack-years), and COPD	Non-small cell lung cancer, squamous cell subtype	Left lung, lower lobe extending to the origin of upper bronchus	Neoadjuvant chemotherapy (3 cycles)	To avoid pneumonectomy
9	M	50	Past smoker (45 pack-years) and COPD	Non-small cell lung cancer, squamous cell subtype	Right lung and extending to proximal bronchi and pulmonary artery	Neoadjuvant chemotherapy (3 cycles)	To avoid pneumonectomy
10	F	79	Middle lobectomy for carcinoid tumor and thyroidectomy	Recurrence of carcinoid tumor	Right lung and extending to proximal bronchi and pulmonary artery	None	To avoid pneumonectomy
11	M	54	Alcohol use disorder, past smoker (60 pack-years), and COPD	Non-small cell lung cancer, squamous cell subtype	Right lung and extending to proximal bronchi and pulmonary artery	Neoadjuvant chemotherapy (3 cycles)	To avoid pneumonectomy
12	F	41	Thyroidectomy and ablation of atrial tachycardia	Carcinoid tumor	Left lung, lower lobe extending to superior pulmonary vein	None	To avoid pneumonectomy
13	M	60	Diabetes, coronary stenting, past smoker (80 pack-years), and COPD	Non-small cell lung cancer, squamous cell subtype	Right lung, lower and middle lobe extending to proximal bronchi	Neoadjuvant chemotherapy (3 cycles)	To avoid pneumonectomy
14	M	59	Cardiac arrhythmia, past smoker (60 pack-years), and COPD	Non-small cell lung cancer, squamous cell subtype	Right lung, lower and middle lobe extending to proximal bronchi	Neoadjuvant chemotherapy (3 cycles)	To avoid pneumonectomy
15	M	68	Endovascular treatment of aortic aneurysm	Non-small cell lung cancer, squamous cell subtype	Left lung, lower lobe extending to the origin of upper bronchus	Neoadjuvant chemotherapy (3 cycles)	To avoid pneumonectomy
16	M	68	Hypertension, past smoker (50 pack-years), and COPD	Non-small cell lung cancer, adenocarcinoma subtype	Left lung, upper lobe extending to main bronchus	Neoadjuvant chemotherapy (3 cycles)	To avoid pneumonectomy
17	M	45	Hypertension and thyroid carcinoma	Athaplastic thyroid carcinoma	Tracheal invasion left in place at initial surgical resection (R2) ^b	None	Extensive lesion and failure of previous treatment
18	F	49	Amygdalectomy	Non-small cell lung cancer, large cell subtype	Left lung, lower lobe extending to the origin of upper bronchus	Neoadjuvant chemotherapy (3 cycles)	To avoid pneumonectomy
19	M	50	Amygdalectomy and past smoker (34 pack-years)	Rhabdomyosarcoma	Right lung and extending to proximal bronchi and thoracic wall	Neoadjuvant chemotherapy (5 cycles)	To avoid pneumonectomy
20	F	64	Recurrent thyroid carcinoma and right vocal cord paralysis	Papillary thyroid carcinoma	Invasion on right side of trachea left in place at iterative surgical resection (R2) ^b	Refractory to iterative iodine therapy	Extensive lesion and failure of previous treatment

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; HSV, herpes simplex virus; ICU, intensive care unit; R2, macroscopic residual tumor.

^a Calculated as weight in kilograms divided by height in meters squared.

^b Found during pathological examination of the resected specimens.

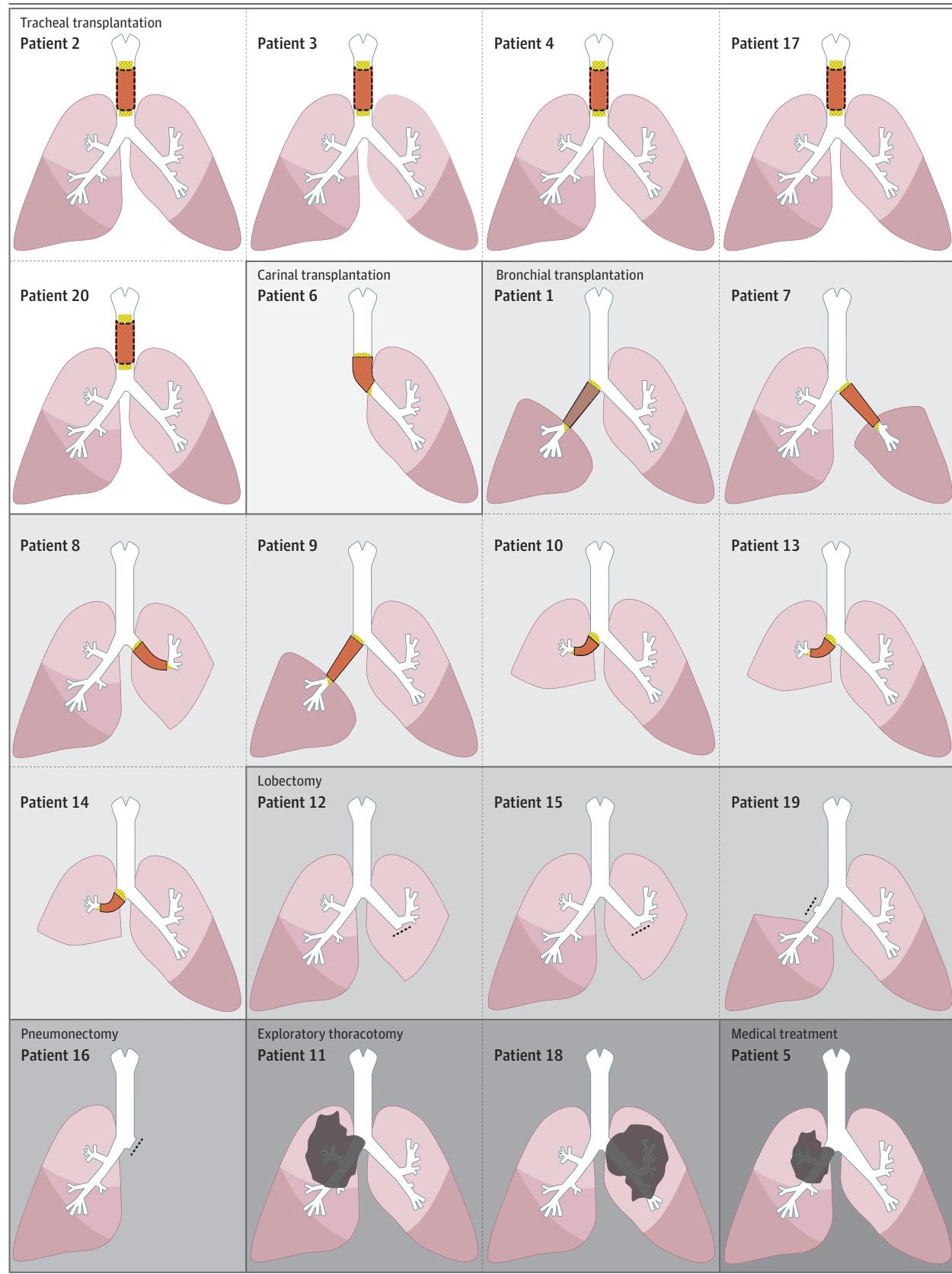
Table 2. Primary and Secondary Outcomes by Type of Intervention

Type of Intervention	Date of Operation	Patient No.	Hospital Length of Stay, d	Primary Outcome: 90-d Mortality	Secondary Outcome: 90-d Morbidity	Cancer Pathology	Type of Postoperative Cancer Treatment
Tracheal transplantation	Oct 2010	2	14	No	No	NA	NA
Tracheal transplantation	Jan 2011	3	11	No	No	NA	NA
Tracheal transplantation	Oct 2011	4	10	No	No	NA	NA
Tracheal transplantation	Jun 2016	17	6	No	Subcutaneous emphysema	RO resection ^a	None
Tracheal transplantation	Feb 2017	20	10	No	Tracheal granuloma, laryngeal edema at months 2 and 3; bronchoscopy, and tracheostomy	RO resection ^a	None
Venovenous ECMO, right pneumonectomy extended to trachea, and carinal transplantation	May 2012	6	NA	Yes on day 1	Cerebrovascular accident and intracranial carotid artery occlusion	Pathological T4N2M0	NA
Intrapерicardial upper bilobectomy and bronchial transplantation	Oct 2009	1	16	No	Atrial fibrillation, acute lung edema, atelectasis, and urinary retention	Pathological T4N0M0	None
Left upper lobectomy and bronchial transplantation	Oct 2012	7	12	No	Atelectasis	Clinical T2N2M0 and pathological T3N0M0	Radiotherapy
Left lower lobectomy and bronchial and pulmonary artery transplantation	Jan 2013	8	8	No	No	Clinical T2N2M0 and pathological T2N1M0	Radiotherapy
Intrapерicardial upper bilobectomy and bronchial transplantation	Mar 2013	9	9	No	No	Clinical T3N1M0 and pathological T3N1M0	None
Right lower lobectomy and bronchial and pulmonary artery transplantation	Dec 2013	10	22	No	Atrial fibrillation and acute respiratory distress syndrome	2 Atypical carcinoid tumors: pathological T3N0M0	None
Lower bilobectomy and bronchial transplantation	Nov 2014	13	12	No	Atelectasis	Clinical T3N0M0 and pathological T3N1M0	Radiotherapy
Lower bilobectomy and bronchial transplantation	Jan 2015	14	9	No	Anemia necessitating blood transfusion	Clinical T3N0M0 and pathological T0N0M0	Radiotherapy
Standard lobectomy but transplantation not performed	Apr 2014	12	10	No	No	Pathological T2N0M0	None
Standard lobectomy but transplantation not performed	Mar 2016	15	6	No	No	Pathological T2N2M0	Radiochemotherapy
Standard lobectomy extended to thoracic wall but transplantation not performed	Jul 2016	19	9	No	No	Clinical T3N0M0 and pathological T3N0M0	Radiotherapy
Pneumonectomy but transplantation not performed	Apr 2016	16	11	No	Atrial fibrillation	Pathological T2N1M0	None
Exploratory thoracotomy but transplantation not performed	Jun 2014	11	8	No	No	Clinical T4N2M0	Radiochemotherapy
Exploratory thoracotomy but transplantation not performed	Jun 2016	18	6	No	No	Clinical T4N2M0	Radiochemotherapy
Myocardial ischemia but operation not performed	Jul 2011	5	NA	No	No	Clinical T3N2M0	NA

Abbreviations: ECMO, extracorporeal membrane oxygenation; NA, not applicable.

^a Indicates no residual tumor was found during pathological examination of the resected specimens.

Figure 2. Schematic Illustrations of the Intervention Performed for Each of the 20 Patients With End-Stage Tracheal Lesions or Proximal Lung Tumors



In patients 12, 15, 16, and 19, dashed lines indicate bronchial sutures. In patients 5, 11, and 18, gray irregular shapes represent unresectable proximal lung tumors.

Table 3. Long-term Follow-up of Patients Who Had a Tracheal or Bronchial Transplantation

Patient No.	Types of Complications During Long-Term Follow-up	Stent Removed?	Last Follow-up ^a	Status	Clinical Status
Tracheal Transplantation					
2	Laryngeal edema and stent bacterial infection	Yes at 15 mo	7 y and 1 mo	Alive	Breathes and speaks normally through newly formed airways
3	Tracheal granuloma and graft malacia requiring repeated bronchoscopies	No	6 y and 10 mo	Alive	Breathes and speaks through a translaryngeal stent
4	Tracheal granuloma and graft malacia requiring repeated bronchoscopies	Yes at 39 mo	6 y and 1 mo	Alive	Breathes and speaks normally through newly formed airways
17	Tracheal granuloma related to the stent requiring bronchoscopy	No	1 y and 6 mo	Alive	No cancer recurrence; breathes and speaks through the stented aortic graft
20	Tracheal granuloma related to the stent requiring bronchoscopy and tracheostomy during months 5-7	Yes at 5 mo	9 mo	Alive	No cancer recurrence; breathes and speaks normally through newly formed airways
Bronchial Transplantation					
1	Bronchial granuloma related to the stent requiring bronchoscopy	No	2 y and 6 mo	Dead	Diffuse metastases
7	Bronchial granuloma related to the stent requiring bronchoscopy	Yes at 15 mo	5 y and 1 mo	Alive	No cancer recurrence; breathes normally through newly formed airways
8	None	Yes at 22 mo	3 y and 2 mo	Dead	No cancer recurrence but had a myocardial infarction
9	Bronchial granuloma related to the stent requiring bronchoscopy	Yes at 22 mo	4 y and 8 mo	Alive	No cancer recurrence; breathes normally through newly formed airways
10	None	Yes at 17 mo	3 y and 11 mo	Alive	No tumor recurrence; breathes normally through newly formed airways
13	None	Yes at 15 mo	3 y	Alive	No cancer recurrence; breathes normally through newly formed airways
14	None	Yes at 14 mo	2 y and 10 mo	Alive	No cancer recurrence; breathes normally through newly formed airways

^aFrom the date of the operation.

Discussion

In this uncontrolled study, airway bioengineering using stented aortic matrices demonstrated feasibility for complex tracheal and bronchial reconstruction. Prospective protocols for surgical innovations before their introduction into clinical practice remain the exception rather than the rule despite international recommendations.²¹

In the field of airway transplantation, recent advances have been associated with important scientific and ethical controversies.^{22,23} In 2014, the International Society of Cell Therapy in association with other regulators and ethics experts proposed specific recommendations for human airway bioengineering.²⁴ Since the establishment of this research initiative in 1997, all investigators have strictly adhered to the international scientific and ethical principles of surgical innovation.²¹

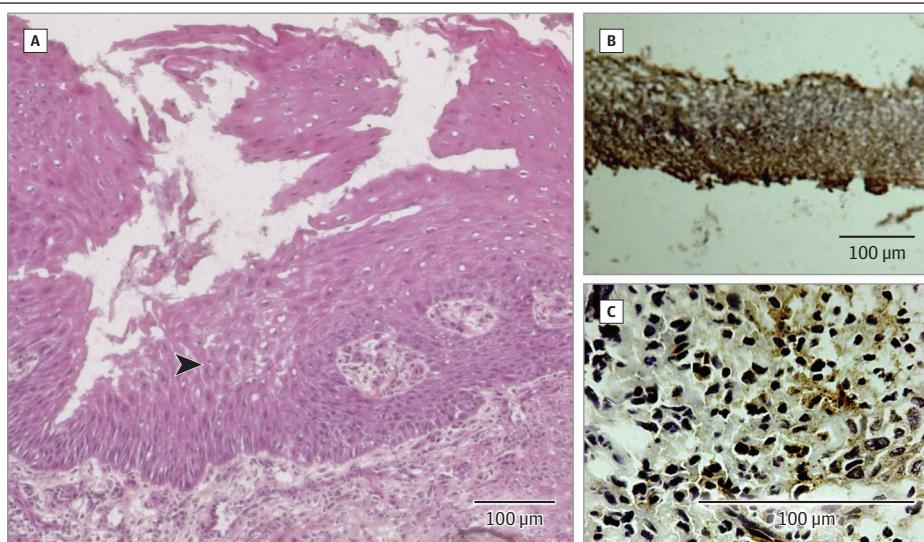
In this study, the 90-day mortality rate was low among patients undergoing the innovative surgical approach. The 90-day mortality rate was used as the primary outcome rather than the 30-day mortality rate because it is more suitable for the evaluation of surgical interventions. The only death reported during the study was observed after a complex carinal reconstruction with extracorporeal membrane oxygenation. However, the mechanism of the cerebrovascular event remains unclear. Despite the fact that the death was not directly associated with the surgical technique, carinal reconstruction should be approached with extreme caution. In a retrospective study²⁵ of 12 patients who had autologous tracheal substitution, the 90-day mortality rate was 16.6%; 2 patients who underwent carinal resection died.

In the present study, the 90-day mortality rate was 0% in the subgroup of patients who underwent bronchial transplantation to avoid a high-risk pneumonectomy. The mortality rate was lower than the rate observed in a retrospective series of patients who required pneumonectomies (varying from 10.5% to 26% at 90 days).^{11,26,27} This is important to note because pneumonectomy remains a frequent operation in the United States and in Europe.²⁸ Tan et al²⁹ developed a closed technique of lung-sparing pulmonary resection of malignant tumors using a different type of tissue-engineered bronchus.

In the subgroup of patients who had tracheal transplantation (n = 5) in the present study, the 90-day mortality rate was 0%. Regarding this mortality rate, it is challenging to compare the results from the present study with those obtained by retrospective case reports or series. Since the review of airway transplantation by Grillo,³⁰ recent advances have been observed and include the development of modern tissue engineering techniques.^{7,24,31,32} The results obtained by Macchiarini et al¹ have been critically debated following the revelation that the majority of patients died after the implantation of tissue-engineered airways, which is in contrast to the initial reports.^{3,5,22-24}

Other case studies have been reported by multiple groups using various conduit types including a Marlex mesh patch with spiral rings covered by a collagen sponge (Omori et al^{33,34}; n = 7),

Figure 3. Histology and Immunohistochemistry of Biopsy Specimens of Aortic Allografts



A, Superficial graft biopsy specimen from patient 2 obtained 15 months after tracheal transplantation showed regeneration of a mixed respiratory neopithelium-like structure (black arrowhead) (hematoxylin-eosin-safran stain). B and C, Cryopreserved aortic allograft biopsy specimens from patient 4 obtained 39 months after tracheal transplantation showed type 2 collagen (B) and Sox9 (C) immunoreactivity (brown). The positive labeling of the cryopreserved aortic allograft for these 2 specific collagen markers suggested the presence of cartilage-like cells. Biopsy specimens from nonimplanted cryopreserved aortic allografts were negative for these markers.

Immunohistochemistry for collagen type 2 used goat polyclonal anticollagen type 2 with horseradish peroxidase (HRP)-labeled polymer-antigoat antibody detection system (Envision+ Kit, Dako K4011), 3,3'-diaminobenzidine (DAB+) as the chromogen (brown-colored precipitate at the antigen site), and Mayer hematoxylin counterstain. Immunohistochemistry for Sox9 used a rabbit polyclonal anti-Sox9 with HRP-labeled polymer-antirabbit antibody detection system (Envision+ Kit, Dako K4011), DAB+ as the chromogen (brown-colored precipitate at the antigen site), and Mayer hematoxylin counterstain.

tracheal allograft after withdrawal of immunosuppressive therapy (Delaere et al^{2,6,35}; n = 6), and a decellularized cadaveric trachea (Elliott et al,⁴ Hamilton et al,³⁶ and Steinke et al³⁷; n = 2). These reports have led some groups to start prospective observational studies.²⁴ The 90-day morbidity rate in the present series was not directly linked to the surgical technique but rather to common complications of thoracic surgery. Importantly, there were no major complications related to the allograft or the stent.

The present study demonstrated positive long-term results. No death was related to airway transplantation using stented cryopreserved aortic allografts. Furthermore, stent removal was feasible in the majority of patients in this study as well as in preclinical studies^{7,11} and in a recent report.¹² The majority of patients were breathing and speaking normally without a tracheostomy or stent at long-term follow-up. Moreover, postoperative examinations did not detect a definitive malacia of the cryopreserved aortic allografts after stent removal.

The present study confirmed prior biological observations.¹² The regeneration of a mixed respiratory epithelium was observed on superficial allograft biopsies. Immunodetection of type 2 collagen, Sox9-specific markers, and engraftment (chimerism) studies from samples of neotissues demonstrated de novo generation of cartilage within the aortic allografts from recipient cells. Aortic matrices played a significant role in this observation as illustrated by the release of proangiogenic, chemoattractant, proinflammatory and immunomodulatory cytokines, and growth factors.¹² The main

hypothesis was that this phenomenon promoted progenitor or stem cell homing followed by de novo generation of cartilage. In this scenario, the human body was used as a natural bioreactor and allowed *in vivo* airway tissue engineering.

The role of stem cells in airway tissue regeneration has been widely debated in recent years. Some have argued that airway regeneration should be regarded as hypothetical and scientifically unfounded.³⁵ To date, there has been no further explanation of the process observed since the beginning of the experiments. The mechanism of epithelium regeneration is less controversial. Epithelial cells have gradually repopulated the allograft lumen by direct migration, by expansion from adjacent native airways (as observed after epithelium destruction), or by both.³⁸

The technique of *in vivo* bioengineering using an aortic matrix has been applied to the replacement of a small bowel segment with encouraging results in a porcine model.³⁹ Compared with other techniques, the present solution did not require the use of decellularized cadaveric tracheal allografts, recipient cells, artificial bioreactors, or immunosuppressive treatment.^{7,24,30-32}

Areas for additional research include the possibility to accelerate de novo generation of cartilage for early stent removal; study of mechanisms of airway regeneration within cryopreserved aortic matrices; assessment of long-term quality of life among patients after receiving a transplantation; and development of clinical applications using multicenter studies, in particular for patients with end-stage tracheal lesions or proximal lung tumors requiring a pneumonectomy.

Limitations

This study has several limitations. First, this is a feasibility study with a limited number of patients. Larger studies are needed for a validated estimate of this technique. Second, along with many surgical innovations, this a monocentric study, which implies that the results cannot be generalized without further evaluation involving a larger number of centers. Third, this is a noncomparative study. Considering these limitations, further studies and multicenter randomized clinical trials are necessary to evaluate the benefit-risk balance of this approach

for specific indications such as end-stage tracheal diseases, locally advanced thyroid cancer, and proximal lung cancer.

Conclusions

In this uncontrolled study, airway bioengineering using stented aortic matrices demonstrated feasibility for complex tracheal and bronchial reconstruction. Further research is needed to assess efficacy and safety.

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