AP-HP.
Hôpitaux universitaires
Paris Seine-Saint-Denis

Fondation Alain Carpentier

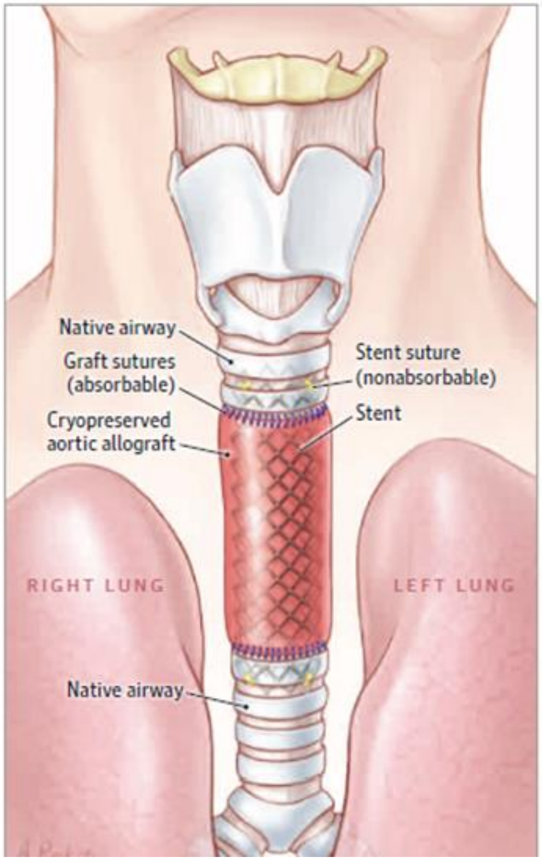
Université Sorbonne Paris Nord

INSERM U1272
H&P
Hypoxie et Poumon

UFR SMBH Santé, Médecine et Biologie Humaine

Pr Emmanuel Martinod, APHP HUPSSD, Université Paris Nord

A Airway transplantation using stented aortic matrix



ELSEVIER

CrossMark

Canadian Association of Radiologists Journal 66 (2015) 30–43

CANADIAN ASSOCIATION OF RADIOLOGISTS JOURNAL

www.carjonline.org

Thoracic and Cardiac Imaging / Imagerie cardiaque et imagerie thoracique

The Wonderful World of the Windpipe: A Review of Central Airway Anatomy and Pathology

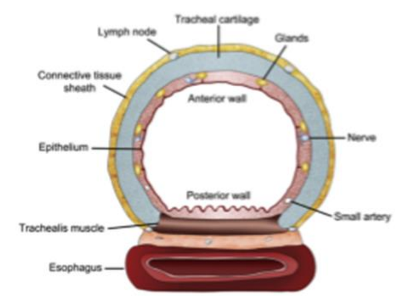
David A. Lawrence, MD[a,*], Brittany Branson, MD[b], Isabel Oliva, MD[c], Ami Rubinowitz, MD[b]

[a]*Department of Radiology and Medical Imaging, University of Virginia School of Medicine, Charlottesville, Virginia, USA*
[b]*Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut, USA*
[c]*Medical Imaging, University of Arizona College of Medicine, Tucson, Arizona, USA*

Table 3

Nonneoplastic and neoplastic causes of focal tracheal narrowing. A useful memory aid to remember the neoplastic causes of focal tracheal narrowing is "CAMPS."

Nonneoplastic	Neoplastic
Post intubation	Carcinoid
Post-infectious (TB, tracheal papillomatosis, Rhinoscleroma)	Adenoid cystic carcinoma
Extrinsic compression	Mucoepidermoid carcinoma
	Pleomorphic adenoma
	Squamous cell carcinoma



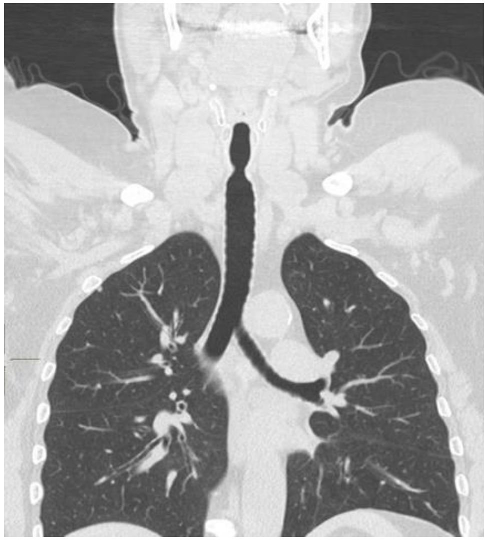
SURGERY OF THE AIRWAYS

Hermes C. Grillo (1923-2006),
the « Father of modern tracheal surgery »

Surgery of the
TRACHEA
and **Bronchi**

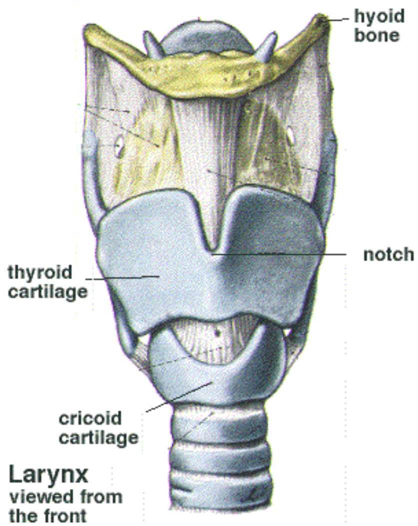
2004
BC Decker Inc
Hamilton • London

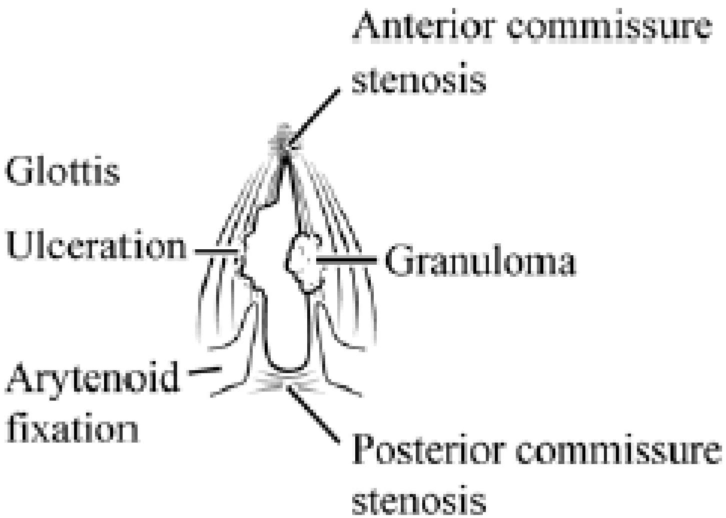
- Data on past medical history
  - Multiple intubations and tracheostomies, prior operative and/or bronchoscopic procedures
- Radiologic study and flexible and/or rigid bronchoscopy
  - Etiology, mechanism, site, length
- Delay of resection
  - “Emergency resection of tracheal lesion is rarely, if ever, needed” - Hermes Grillo
- Systemic considerations



- **Is the larynx competent or not ?**

"Serious complications may result if a surgeon repairs the trachea without prior assurance of laryngeal competence" Grillo, Surgery of the trachea and bronchi, 2004

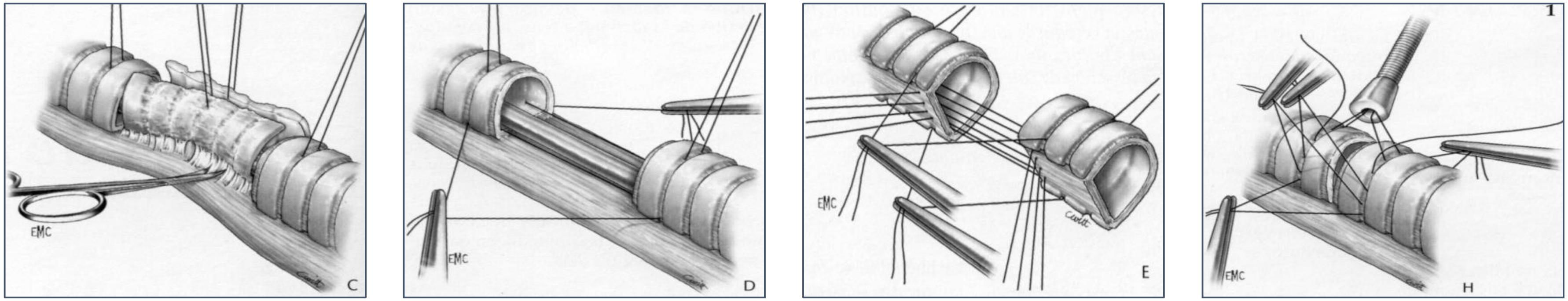


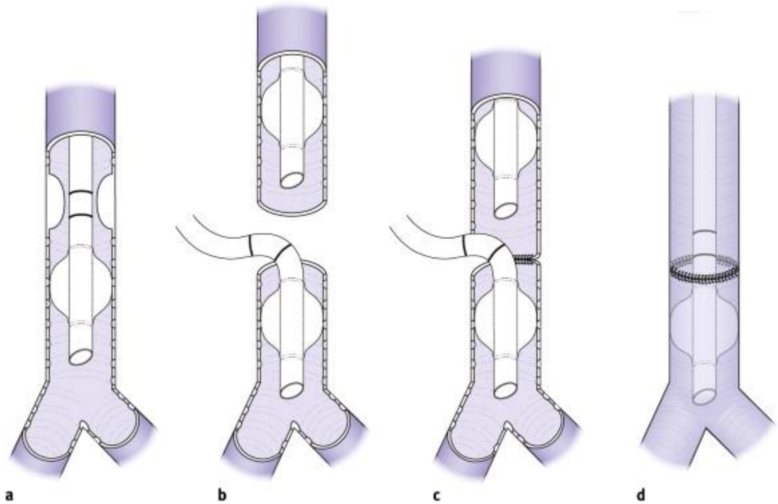


- **Will resection and reconstruction likely exceed safe limits?**

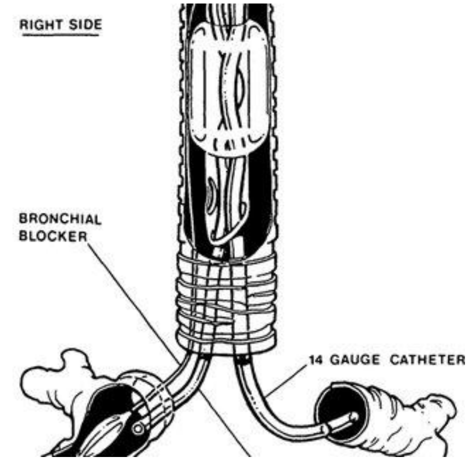
One-half of the adult trachea can be resected with primary reconstruction

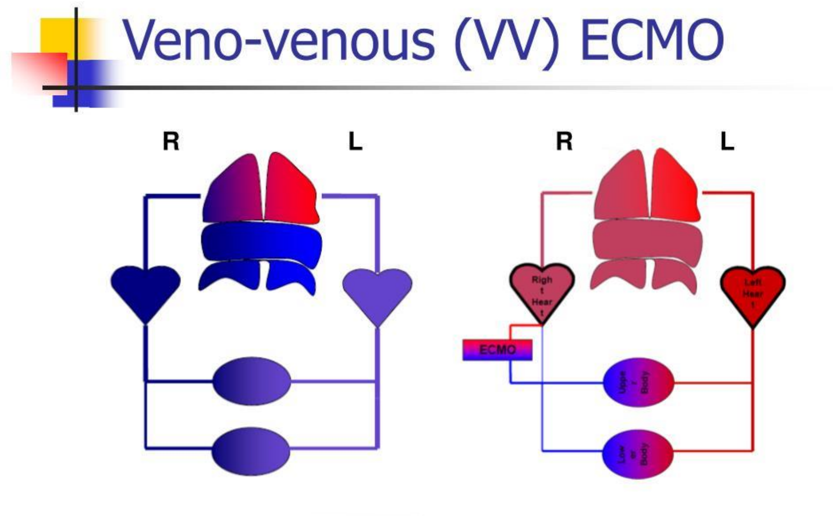
This theoretical limit can change with : age, anatomical characteristics, type of lesions and previous treatments



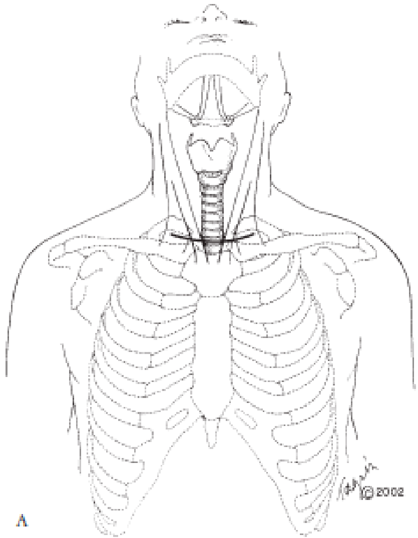


THORACIC ANAESTHESIA
VOLUME 12, ISSUE 12, P558-562, DECEMBER 01, 2011
Anaesthesia for surgery of the trachea and main bronchi
Alistair Macfie, Christopher Hawthorne



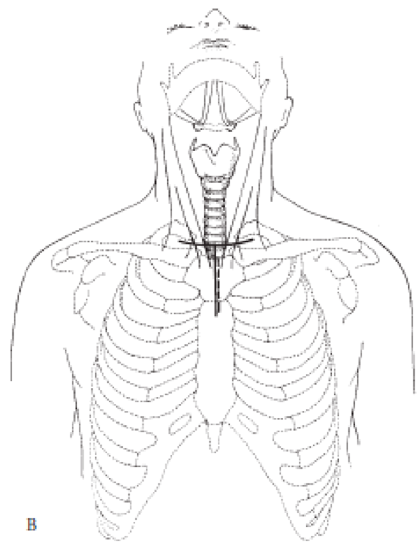


SURGICAL APPROACHES



A

FIGURE 23-1 *Incisions for approach to the upper trachea. A, A collar incision is electively placed 1 cm above the clavicular heads. Length is determined by the extent of superior exposure required. B, Extension for upper mediastinal access (cervicomediastinal resection). The vertical arm of the cutaneous incision reaches just below the sternal angle. The sternum is also divided just beyond the angle (dashed line). It is unnecessary to divide the bone laterally at the distal end since it will fracture appropriately as the retractor is opened. C, An apron incision allows the same access but removes most of the incision from the neck.*



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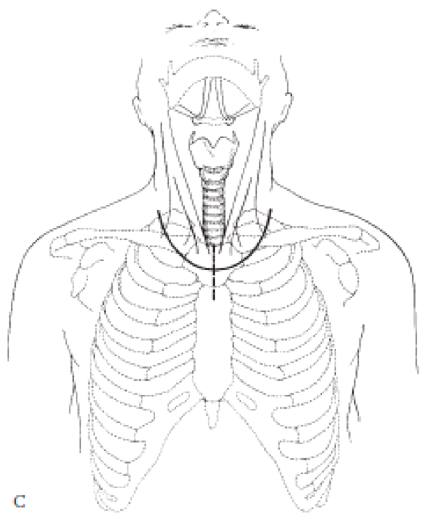
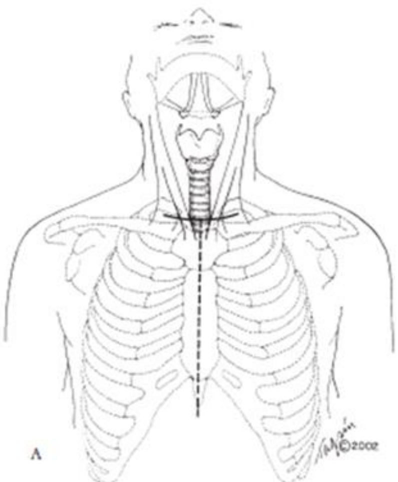


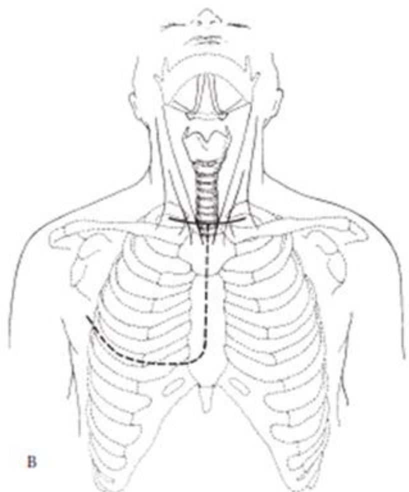
C

SURGICAL APPROACHES

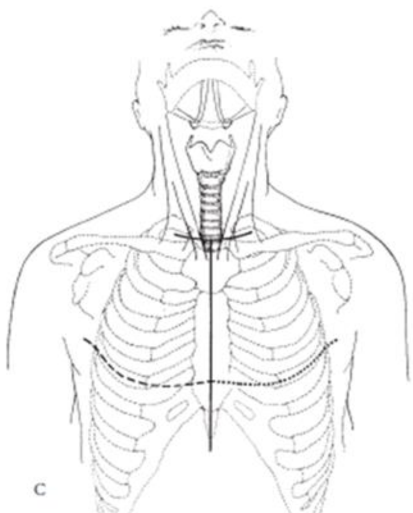


A

FIGURE 23-3 *Extended tracheal resection. A, Complete sternotomy. The cervical incision is still needed for exposure of the upper trachea and larynx. Access to the lower trachea and carina is made possible. B, Incision permitting access to the entire trachea from the larynx to the carina. The cutaneous incision* (dashed line) *is submammary and the thoracic wall incision lies in the fourth interspace. The pectoralis muscle is elevated with the cutaneous flap. C, Further variations in access. Either right or left hemithoraces may be exposed by lateral extensions into fourth interspaces, if sternotomy is inadequate.*



B



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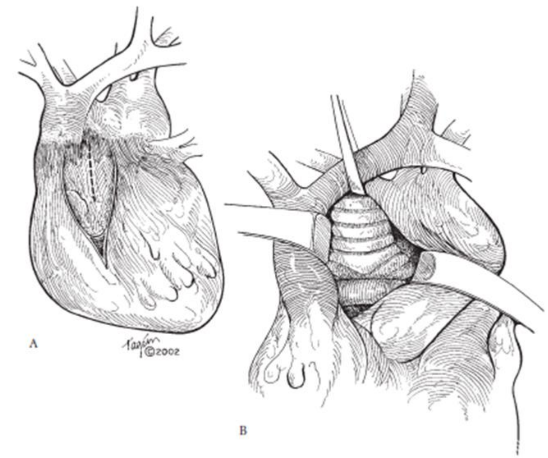


FIGURE 23-6 *Transmediastinal approach to the entire trachea. The sternum is fully divided, as shown in Figure 23-3C. A, The anterior pericardium is opened vertically between the superior vena cava and the aorta. The posterior pericardium is similarly opened* (dashed line). *B, Retraction of the vena cava and aorta exposes a quadrilateral space in which the lower trachea and carina are seen. A tape around the brachiocephalic artery and vein helps exposure. The right pulmonary artery lies just below the carina.*

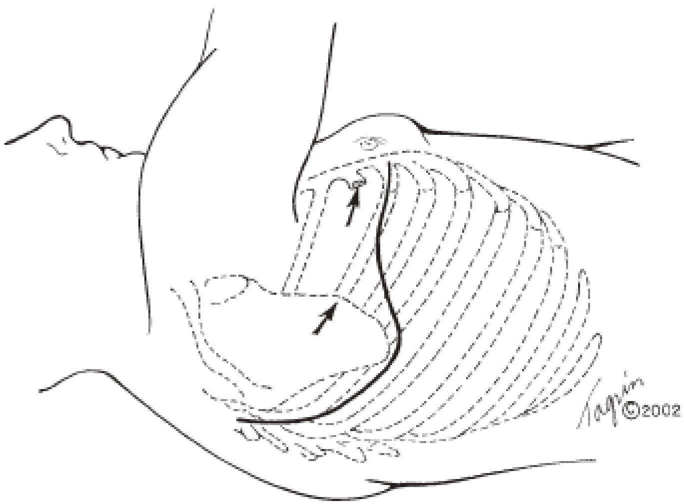
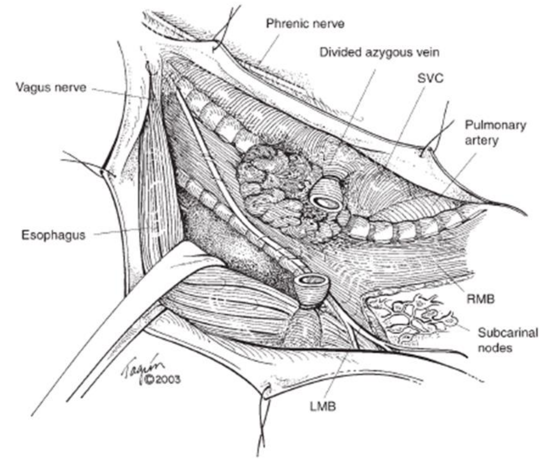
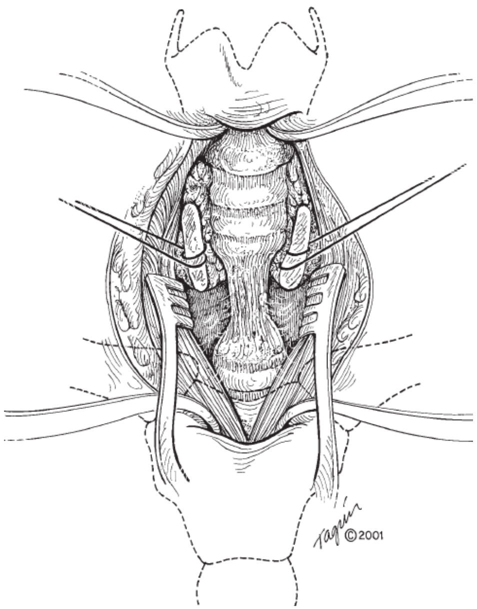
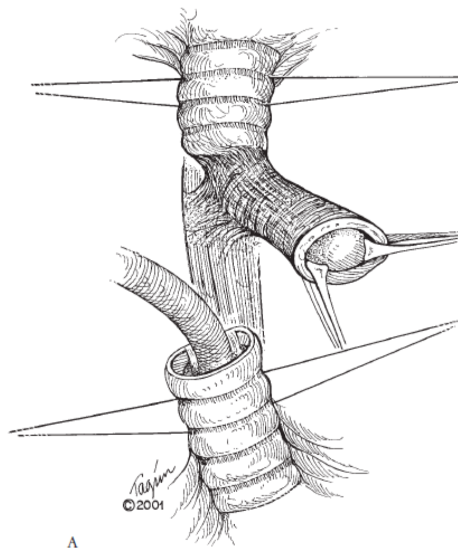


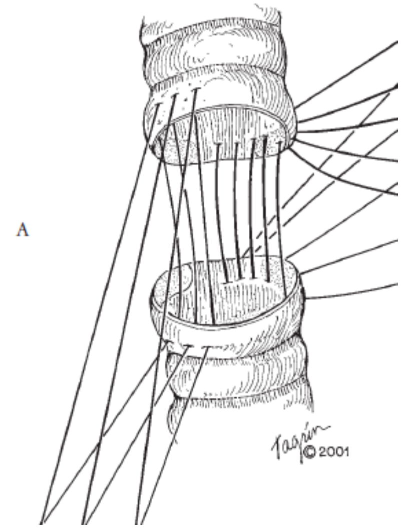
FIGURE 23-7 *Transthoracic approach provides excellent access to the lower trachea and carina, including the left main bronchus. The posterior cutaneous incision lies midway between the vertebral spine and posterior scapular border. The incision curves beneath the scapular tip, is directed transversely forward, and then curves inferiorly in its anterior portion, in order to overlie the anterior portion of the fourth and fifth ribs; hence, the "Lazy S" configuration of the incision. Individuals vary, but resection of the fourth rib is usually optimal (*anterior arrow*). For airway dissection of any complexity, a posterolateral thoracotomy has been found to be more advantageous than a limited thoracotomy.*

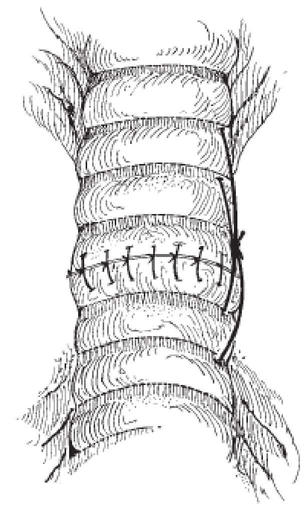


RESECTION + DIRECT END-TO-END ANASTOMOSIS





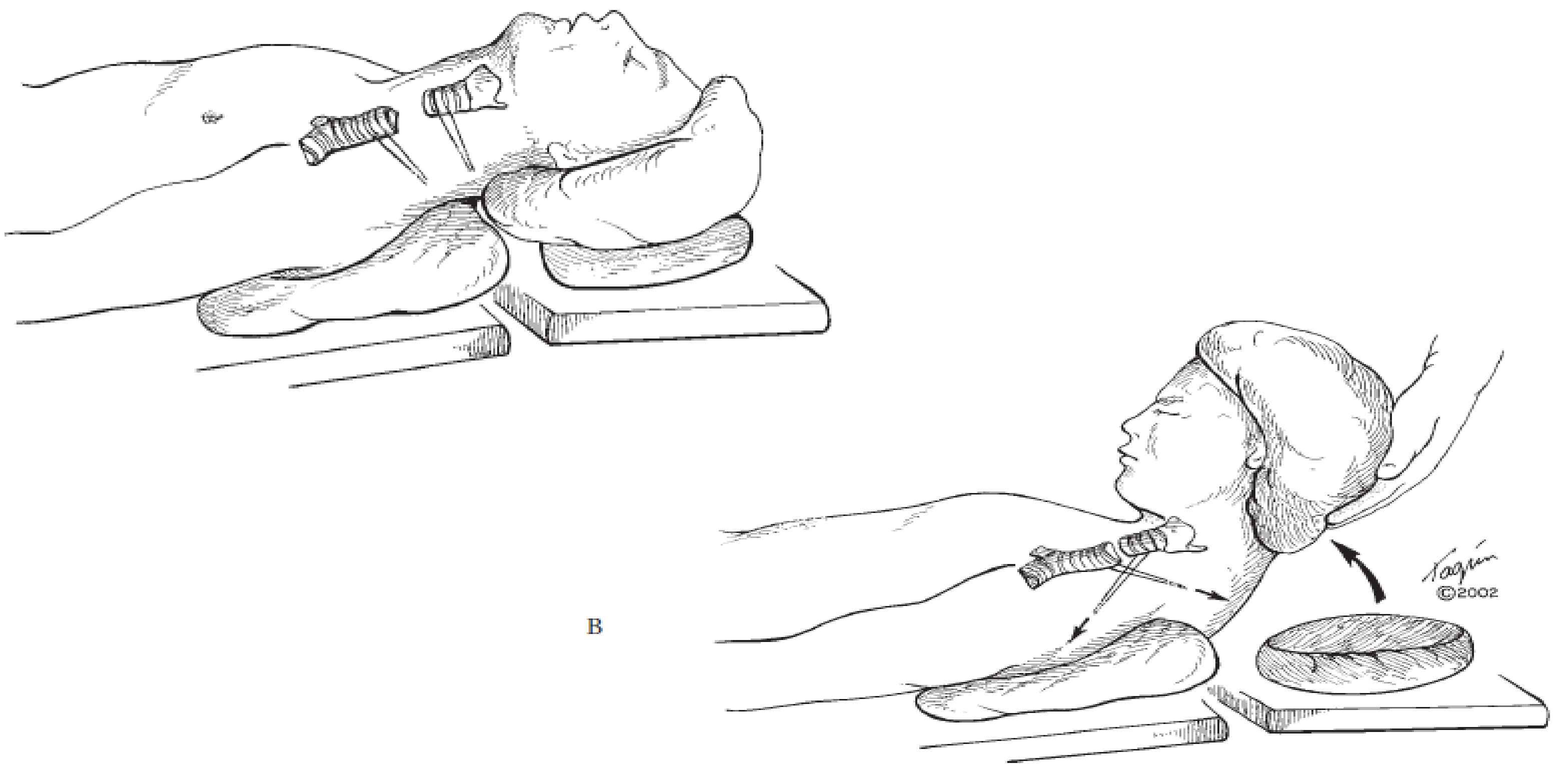




PRETRACHEAL MOBILIZATION AND CERVICAL FLEXION

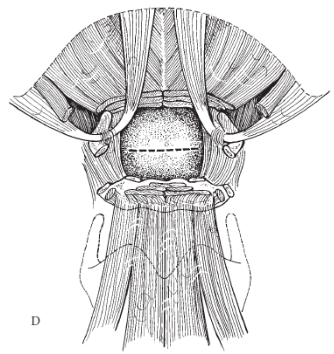
A

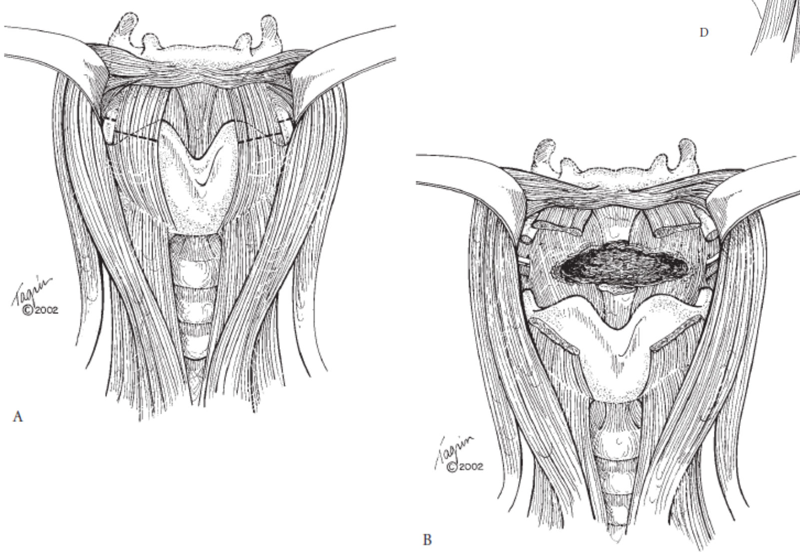
B



RELEASE MANEUVERS

Suprahyoid laryngeal release
Technique of Montgomery





Thyrohyoid laryngeal release procedure
Technique of Dedo and Fishman

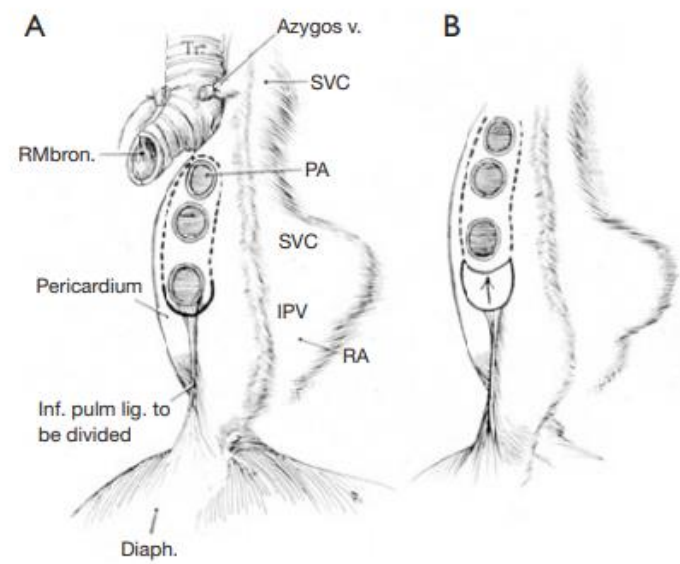
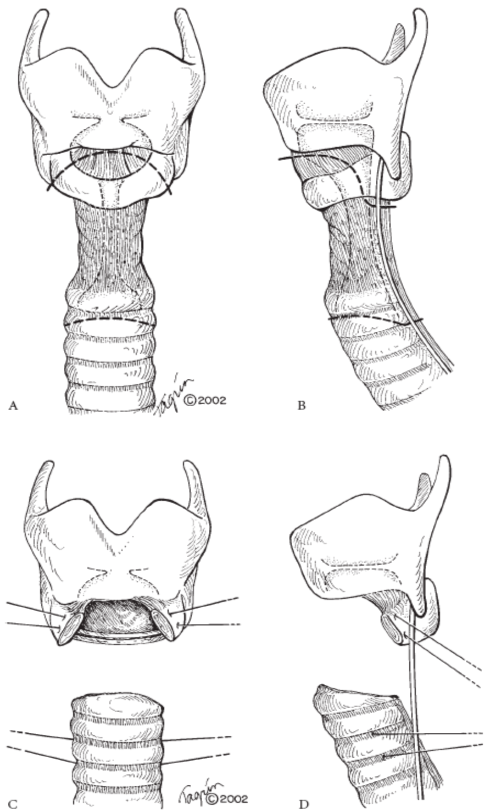


Figure 3 The pericardium can be opened circumferentially around the hilum after the inferior pulmonary ligament is divided (A). The arrow depicts the cephalad displacement of the hilum after circumferential hilar release (B). SVC, superior vena cava; PA, pulmonary artery; IPV, inferior pulmonary vein; RA, right atrium; Tr, Trachea.

Ann Cardiothorac Surg 2018;7(2):293-298

LARYNGOTRACHEAL LESIONS



PEARSON

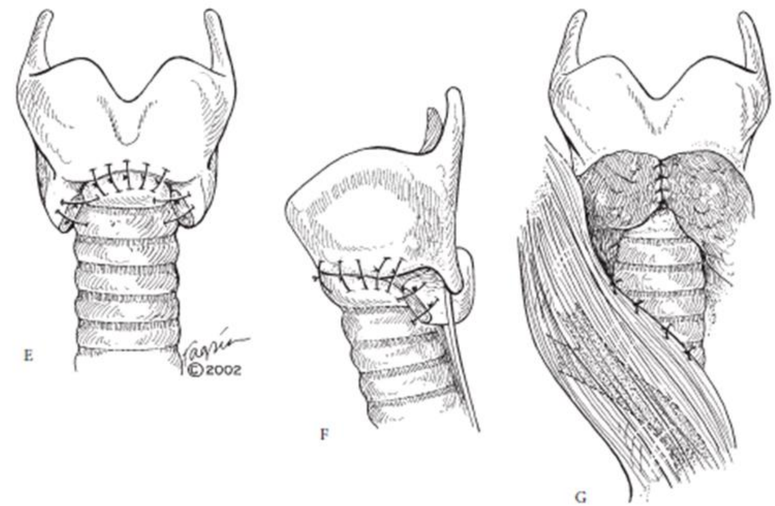


FIGURE 25-2 (CONTINUED) E, F, *Completed anastomosis. Anastomotic sutures are placed as described in Chapter 24, "Tracheal Reconstruction: Anterior Approach and Extended Resection," for tracheotracheal anastomosis. Posteriorly, because of the thickness of the cricoid plate, sutures often traverse only part of the cartilage's thickness, but enter the airway lumen through full thickness of mucous membrane. Stay sutures are approximated first, as described in Chapter 24, "Tracheal Reconstruction: Anterior Approach and Extended Resection." They are omitted in the illustration for clarity. Some overriding of the cut edges of lateral cricoid laminae and trachea often occurs.* G, *The anastomosis is usually covered with reapproximated thyroid isthmus or strap muscles, which are sutured together over it and to the larynx and trachea above and below the anastomosis. The right sternohyoid muscle may be sutured to the trachea over the brachiocephalic artery, as shown, for its protection. The site of a potential tracheostomy in the triangle between the covered anastomosis and the artery will be marked with a single fine suture.*

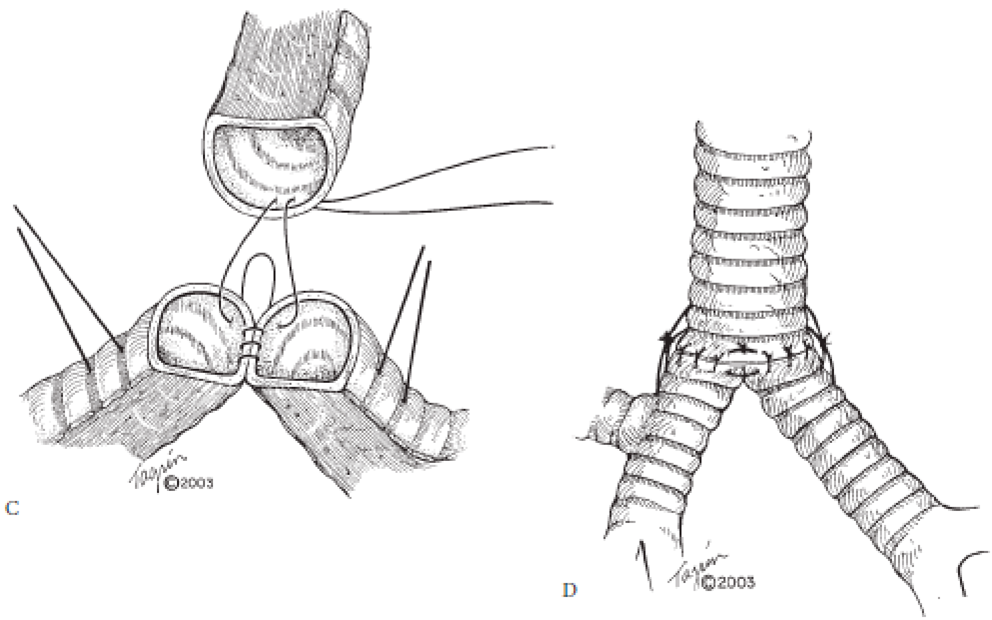


FIGURE 29-1 (CONTINUED) C, *After the neocarina is completed, sutures for anastomosis between the trachea and the bronchial circumference are placed. The joined main bronchi are treated as a single unit. Sutures will be closer together on the tracheal side since the bronchial circumference is longer. Sutures are placed proportionally; the tracheal and bronchial edges are not tailored. The anterior cartilaginous wall sutures are placed first. The anterior mattress suture at the confluence of the trachea and both bronchi is shown. The balance of the anterior anastomotic sutures is serially placed on both sides, from the midpoint to the lateral traction sutures, arrayed on each side in the order of placement. These will be tied in reverse order of placement. Membranous wall sutures are placed next. A mattress suture is also used at the posterior confluence. Midlateral stay sutures in the trachea are not shown. If this anastomosis is performed through a median sternotomy (with partial pericardiotomy), the membranous wall sutures are placed first, with half ranged to either side. The anterior sutures are then placed. Traction sutures are tied before the anastomotic sutures.* D, *After all anastomotic sutures are placed, the paired lateral traction sutures are tied on each side simultaneously. Cervical flexion is maintained during this maneuver. Anastomotic sutures are tied, beginning with the most accessible ones in the cartilaginous wall posterior to the traction sutures. This will further reduce any residual tension as the next sutures are tied, since the membranous wall tears more easily. As each suture is tied, excess suture is removed. Membranous wall sutures are tied next, followed by anterior sutures. Note the mattress suture in the anterior midpoint.*

Postintubation Tracheal Stenosis: Management and Results 1993 to 2017

Cameron D. Wright, MD, Shuben Li, MD, Abraham D. Geller, MD, Michael Lanuti, MD, Henning A. Gaissert, MD, Ashok Muniappan, MD, Harald C. Ott, MD, and Douglas J. Mathisen, MD

Division of Thoracic Surgery, Massachusetts General Hospital, Boston, Massachusetts; Department of Thoracic Surgery, First Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China; and Harvard Medical School, Boston, Massachusetts

MASSACHUSETTS GENERAL HOSPITAL
THORACIC SURGERY

Table 7. Comparison Outcomes Postintubation Tracheal Stenosis Massachusetts General Hospital Experience

	1993-2017				1965-1992			
Outcome	No.	Good/ Satisfactory (% [n])	Failure (% [n])	Death (% [n])	No.	Good/ Satisfactory (% [n])	Failure (% [n])	Death (% [n])
All patients	392	93 (365)	6 (24)	0.8 (3)	503	93.7 (471)	4 (20)	2.4 (12)
TRR	301	96 (289)	3.3 (12)	3 (1)	441	94.1 (415)	3.2 (14)	2.7 (12)
LTR	91	85 (77)	15 (14)	0 (0)	62	90 (56)	8 (4)	1.6 (2)
Redo TRR	45	91 (41)	9 (4)	0 (0)	53	89 (47)	7.5 (4)	3.8 (2)
Reintubation	19	65 (12)	25 (5)	10 (2)	23	46 (11)	24 (5)	30 (7)
No prior treatment	31	97 (30)	...	3 (1)	342	91.5 (313)	6.1 (21)	2.3 (8)

Data derived from Grillo and colleagues.[7]

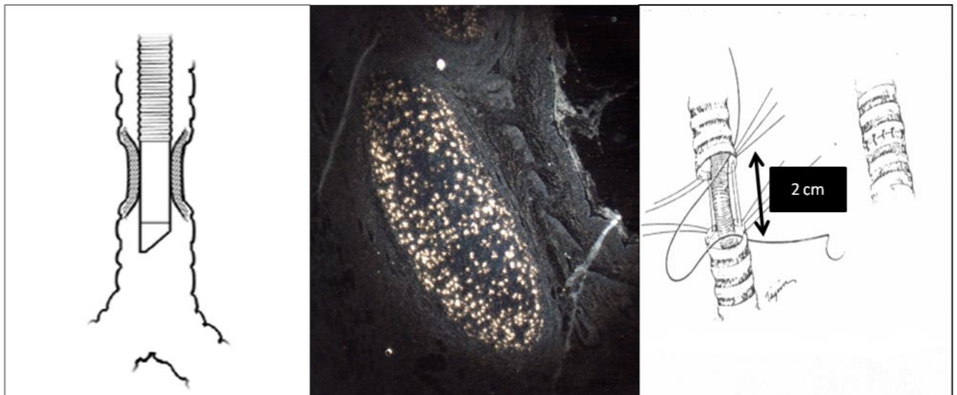
LTR, laryngotracheal resection; No., number; TRR, tracheal resection and reconstruction.

Feasibility of Airway Transplantation Using a Bioengineered Stented Aortic Allograft

JAMA. 2018 Jun 5;319(21):2212-2222

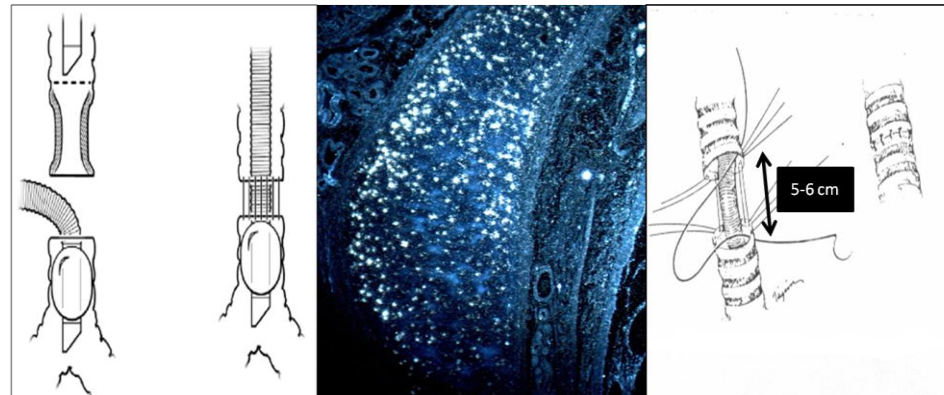
TRACHEAL RECONSTRUCTION

BEFORE 1960 : inhibition

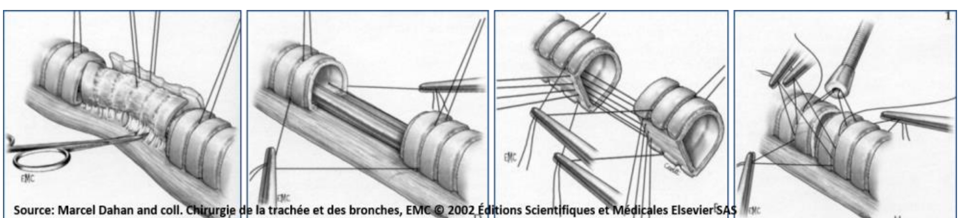


PEROPERATIVE VENTILATION | CARTILAGE: POOR HEALING CAPACITY | THE « 2-CM RULE »

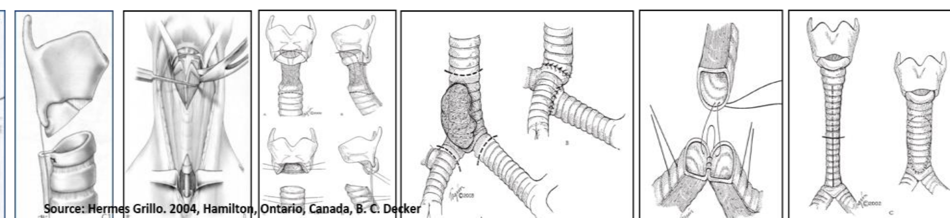
AFTER 1960 : development



PROGRESS IN SURGERY AND ANESTHESIOLOGY : TRACHEAL RECONSTRUCTION FOR LESIONS UP TO 5-6 CM



LESIONS ≤ 5-6 CM : TRACHEAL RESECTION FOLLOWED BY DIRECT END-TO-END ANASTOMOSIS



TRACHEAL PLASTY, LARYNGEAL MOBILIZATION, RESECTION EXTENDED TO LARYNX OR CARINA, CONGENITAL LESIONS

All problems have been solved…

Feasibility of Airway Transplantation Using a Bioengineered Stented Aortic Allograft

JAMA. 2018 Jun 5;319(21):2212-2222

…except one: the treatment of extensive lesions

> ½ length in adults (5-6cm), adenoid cystic carcinoma +++

Limits depending upon age, body build, local anatomy, pathology and prior treatment

TRACHEAL RESECTION + END-TO-END ANASTOMOSIS
Not possible or associated with a high morbi-mortality rate

Palliative treatment
(radiotherapy, chemotherapy, stent)

↓

AIRWAY SUBSTITUTE

Personal unpublished data, P. Joudiou, E. Martinod

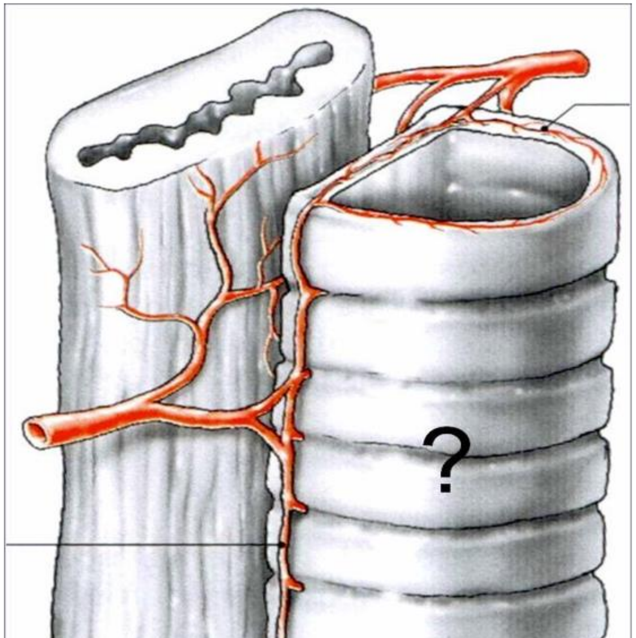
Feasibility of Airway Transplantation Using a Bioengineered Stented Aortic Allograft

JAMA. 2018 Jun 5;319(21):2212-2222

THE CHALLENGE OF AIRWAY REPLACEMENT

A SURGICAL AND BIOLOGICAL CHALLENGE

"It seems so simple to replace a conduit intended primarily for the passage of gases to and from the lung" *Grillo HC, Surgery of the Trachea and Bronchi, 2004*



Source: Marcel Dahan and coll. Chirurgie de la trachée et des bronches, EMC © 2002 Éditions Scientifiques et Médicales Elsevier SAS

REQUIREMENTS
FOR TRACHEAL REPLACEMENT

Rigid and flexible tube

Biocompatible
Non toxic
Non immunogenic
Non carcinogenic

Should - facilitate ré-épithelialization
- integrate to adjacent tissues
- avoid stenosis
- avoid bacterial colonization
- avoid accumulation of mucus
- be stable with time
(no dislocation, no erosion)

Feasibility of Airway Transplantation Using a Bioengineered Stented Aortic Allograft

JAMA. 2018 Jun 5;319(21):2212-2222

Airway Transplantation

-Patients with large or complex airway defects that cannot be repaired primarily

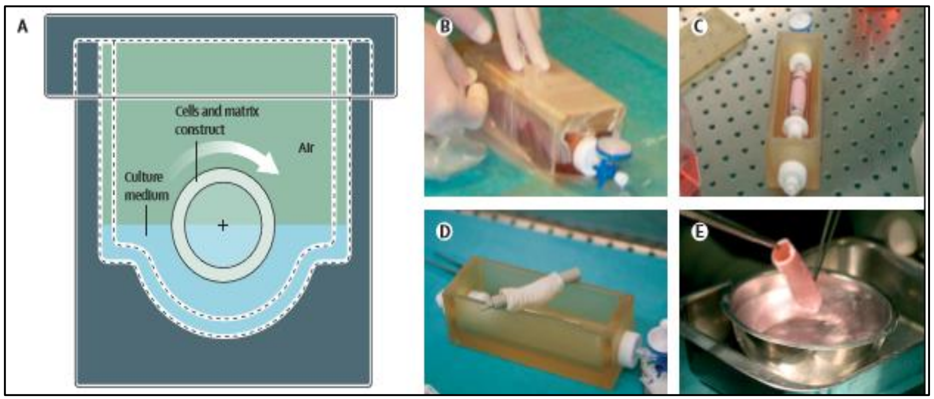
-Trachea, carina, bronchi – benign or malignant lesions

-Case reports or small retrospective studies

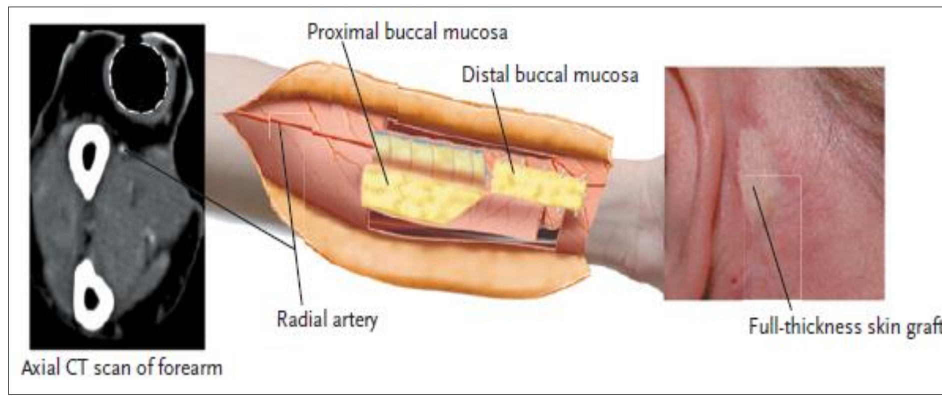
-Bioengineered substitutes, allotransplantation after heterotopic revascularization

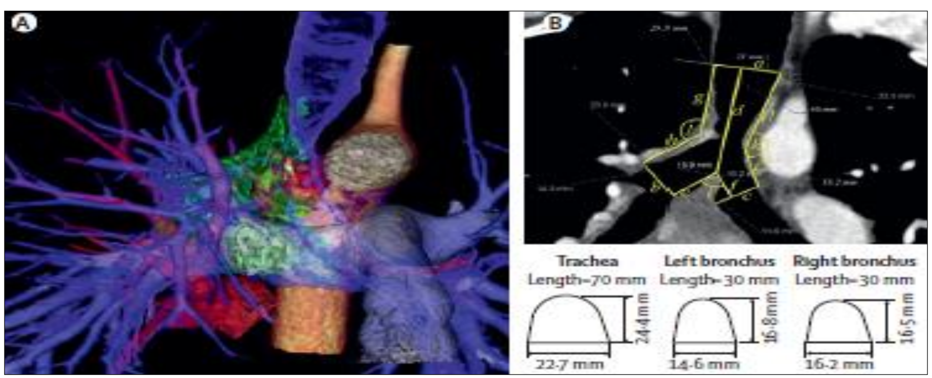
-Failed to achieve standard of care status due to the lack of prospective data in larger series

EUROPEAN GROUP Lancet. 2008;372:2023-30

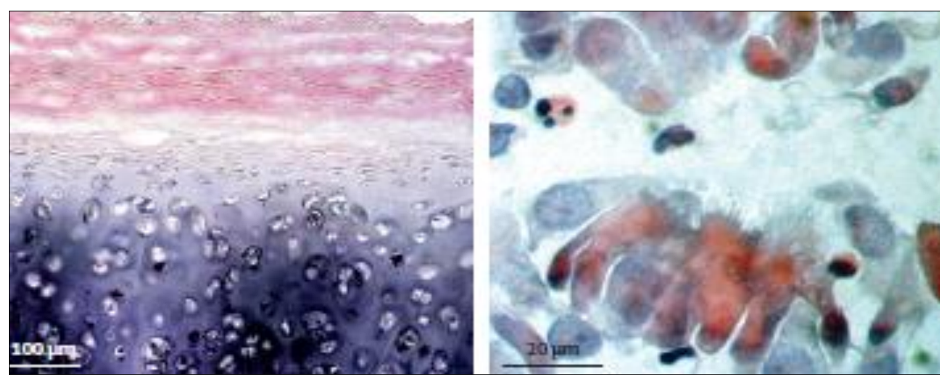


LEUVEN GROUP (DELAERE) N Engl J Med. 2010;362:138-45





MACCHIARINI GROUP Lancet. 2011;378:1997-2004 RETRACTED



LONDON GROUP (ELLIOTT, BIRCHALL) Lancet. 2012;380:994-1000

Feasibility of Airway Transplantation Using a Bioengineered Stented Aortic Allograft

JAMA. 2018 Jun 5;319(21):2212-2222

Airway Transplantation – A major clinical challenge

A reassessment of tracheal substitutes—a systematic review

Brooks Udelsman[1], Douglas J. Mathisen[2], Harald C. Ott[2] *Ann Cardiothorac Surg* 2018;7(2):175-182

[1]Division of General Surgery, [2]Division of Thoracic Surgery, Massachusetts General Hospital, Boston, MA, USA

"The need for tracheal substitution remains a difficult clinical problem without an ideal prosthetic or graft material"

Table 1 Methods of tracheal substitution

Method	Mechanism	Advantages	Disadvantages
Allotransplantation	Donor trachea undergo several weeks of heterotopic revascularization prior to implantation as a tracheal conduit	Structural and mechanical properties or native tissue Can be revascularized	Requires donor Several weeks of heterotopic revascularization Requires period of immunosuppression
Autologous tissue reconstruction	Tubularized autologous tissue with vascular pedicle supported by a stent +/− additional support with harvested costal cartilage	No need for immunosuppression Potentially single day procedure Retains blood supply	Technically difficult Lack of mucociliary clearance Donor site morbidity
Aortic homograft reconstruction	Fresh or banked aortic homograft implanted as a tubularized conduit generally with a supporting stent	Off-shelf availability No need for immunosuppression	Lack of mucociliary clearance No robust blood supply
Tissue engineering	Biodegradable scaffold or decellularized donor trachea seeded with autologous stem cells. Theoretically the stem cells differentiate and recruit circulating cells to repopulate the graft	No need for immunosuppression Possibility of growth potential	Difficult to revascularize *Ex vivo* cell seeding +/− cell line expansion

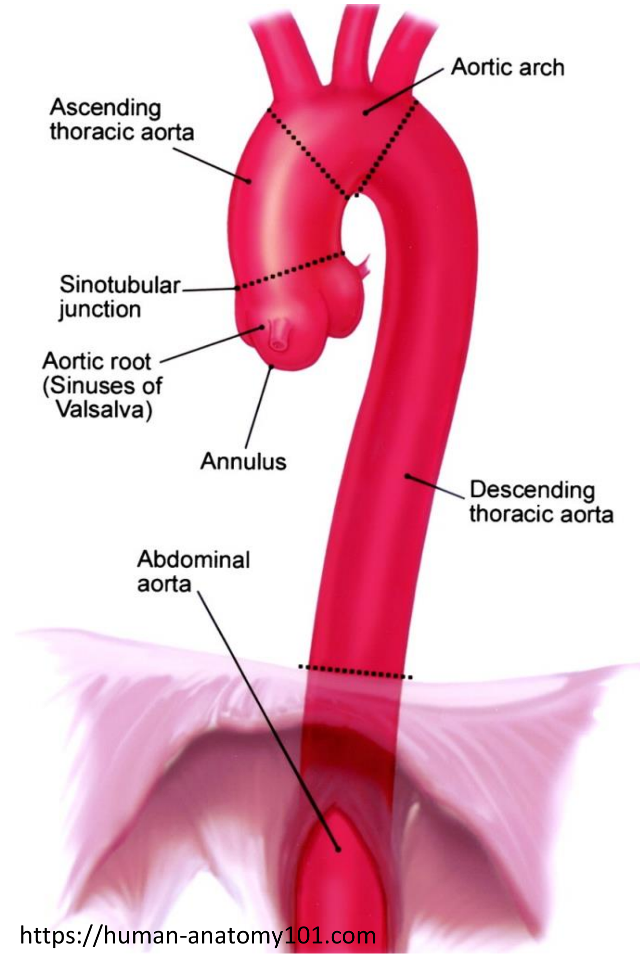
Feasibility of Airway Transplantation Using a Bioengineered Stented Aortic Allograft

JAMA. 2018 Jun 5;319(21):2212-2222

Airway Transplantation Using Stented Aortic Matrices

-1997: research program (Alain Carpentier Foundation)

-7 preclinical studies: autologous and fresh or cryopreserved aortic allografts could be valuable airway substitutes (Martinod and coll.)



https://human-anatomy101.com

AORTA = MATRIX

Advantages:

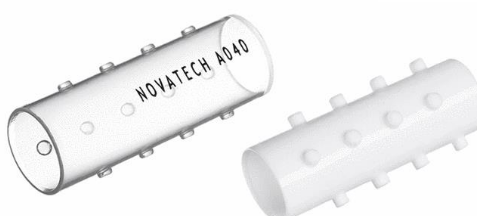
-circular, similar diameter

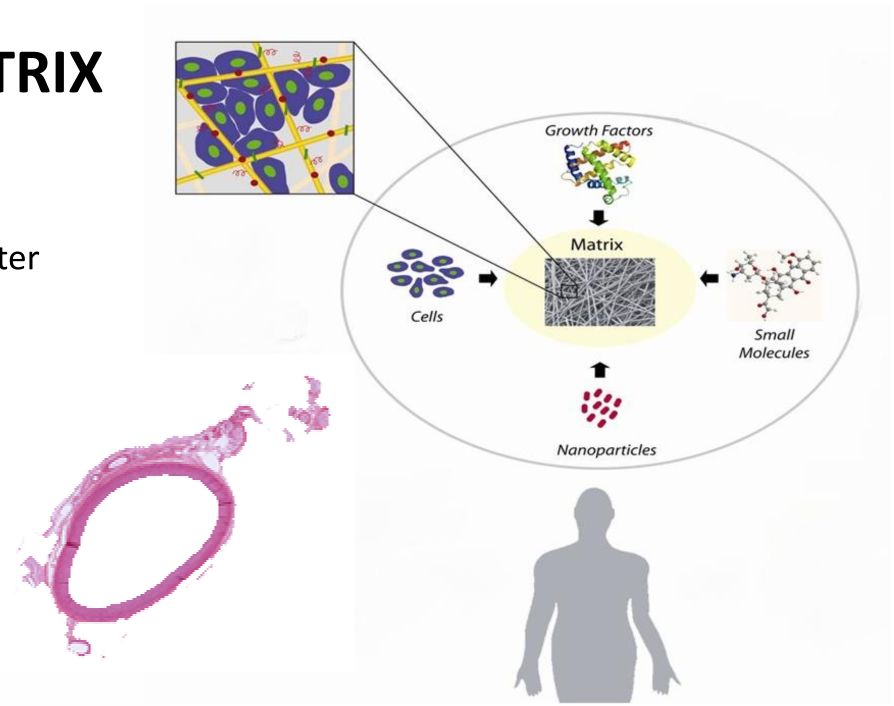
-strength, elasticity

-resistance to infection

Disadvantage:

-collapse : STENT

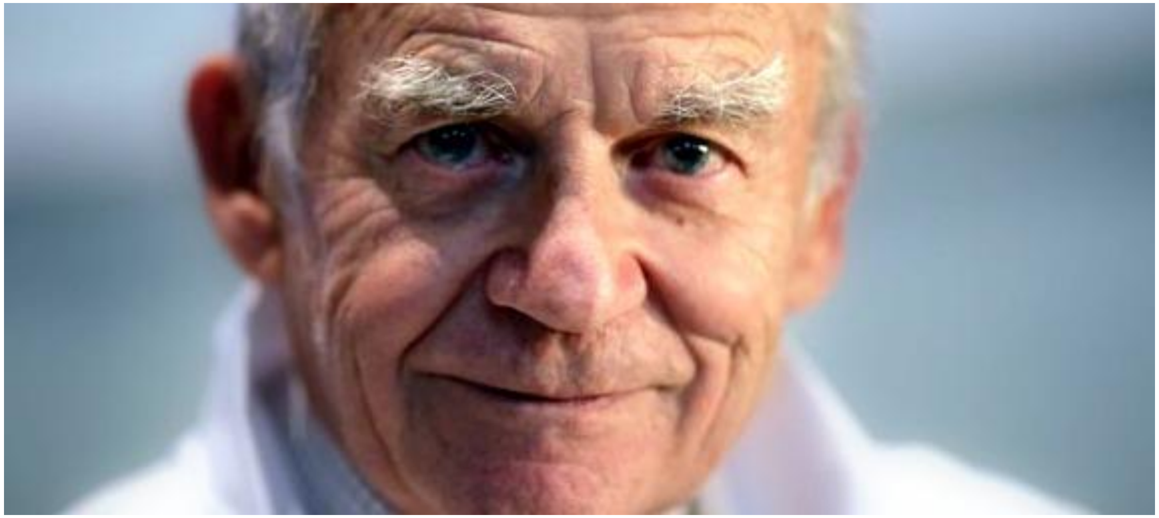




In Vivo Tissue Engineering

Nanotechnological strategies for engineering complex tissues. Dvir T et al. Dec 12, 2010

JAMA. 2018 Jun 5;319(21):2212-2222



Prof Alain Carpentier, Paris - France

Feasibility of Airway Transplantation Using a Bioengineered Stented Aortic Allograft

JAMA. 2018 Jun 5;319(21):2212-2222

Airway Transplantation Using Stented Aortic Matrices

-1997: research program (Alain Carpentier Foundation)

-7 preclinical studies: autologous and fresh or cryopreserved aortic allografts could be valuable airway substitutes (Martinod and coll.)

-Regeneration of epithelium and de novo generation of cartilage: stent removal after 6 months

STEP 1 : AUTOLOGOUS ARTERIAL GRAFT

Métaplasie de tissu aortique en tissu trachéal. Perspectives chirurgicales

Emmanuel Martinod[a]*, Gilbert Zakine[a], Paul Fornes[a], Rachid Zegdi[a], Alexandre d'Audiffret[a], Bertrand Aupecle[a], Nathalie Goussef[a], Jacques Azorin[b], Juan-Carlos Chachques[a], Jean-Noël Fabiani[a], Alain Carpentier[a]

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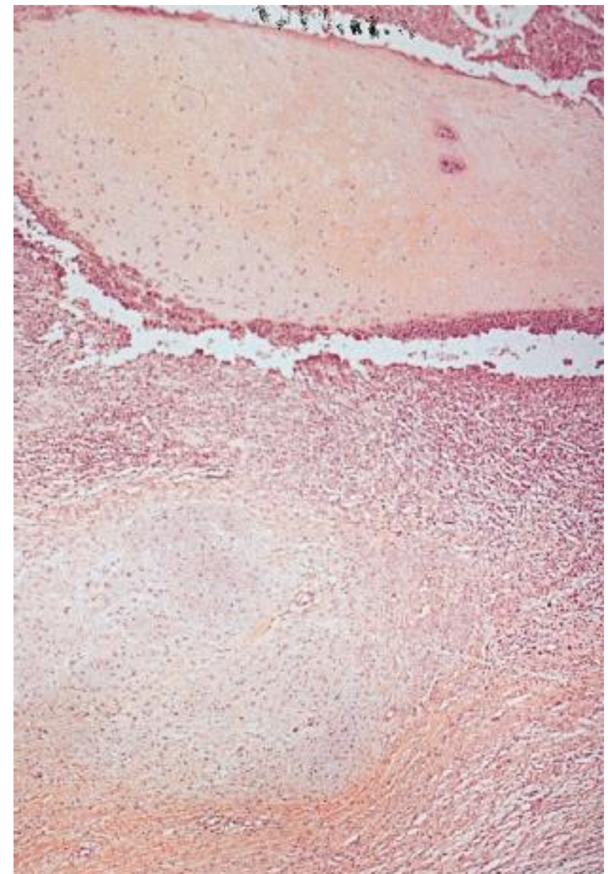
Received 15 novembre 1999; accepted 16 mars 2000

Communicated by Alain Carpentier

Abstract – Metaplastic transformation of an aortic autograft into a tracheal tissue. Surgical implications. Tracheal reconstruction after extensive resection remains an unsolved surgical problem. Numerous attempts have been made using tracheal grafts or prosthetic conduits with disappointing results. In this study, we propose a new alternative using an aortic autograft as tracheal substitute. In a first series of experiments, a half circumference of two rings was replaced with an autologous carotid artery patch. In a second series, a complete segment of trachea was replaced with an autologous aortic graft supported by an endoluminal tracheal stent. No dehiscence or stenosis was observed. Microscopic examinations at 3 and 6 months showed the replacement of the aortic tissue by tracheal tissue comprising neoformation of cartilage and mucociliary or non-keratinizing metaplastic polystratified squamous epithelium. Although these results need to be confirmed by a larger series of experiments, they showed that a vascular tissue placed in a different environment with a different function can be submitted to a metaplastic transformation which tends to restore a normal structure adapted to its new function. These remarkable findings offer new perspectives in tracheal reconstruction in human. © 2000 Académie des sciences/Éditions scientifiques et médicales Elsevier SAS



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-Regeneration of epithelium and de novo generation of cartilage: stent removal after 6 months

STEP 2 : AUTOLOGOUS AORTIC GRAFT

Long-Term Evaluation of the Replacement of the Trachea With an Autologous Aortic Graft

Emmanuel Martinod, MD, Agathe Seguin, MD, Karel Pfeuty, MD, Paul Fornes, MD, Marianne Kambouchner, MD, Jacques F. Azorin, MD, and Alain F. Carpentier, MD, PhD

Laboratoire d'Etude des Greffes et Prothèses Cardiaques, Hôpital Broussais, Upres 264, Université Paris 6, France, and Department of Thoracic and Vascular Surgery, Hôpital Avicenne, Assistance Publique-Hôpitaux de Paris and UFR SMBH, Bobigny, Université Paris 13, France

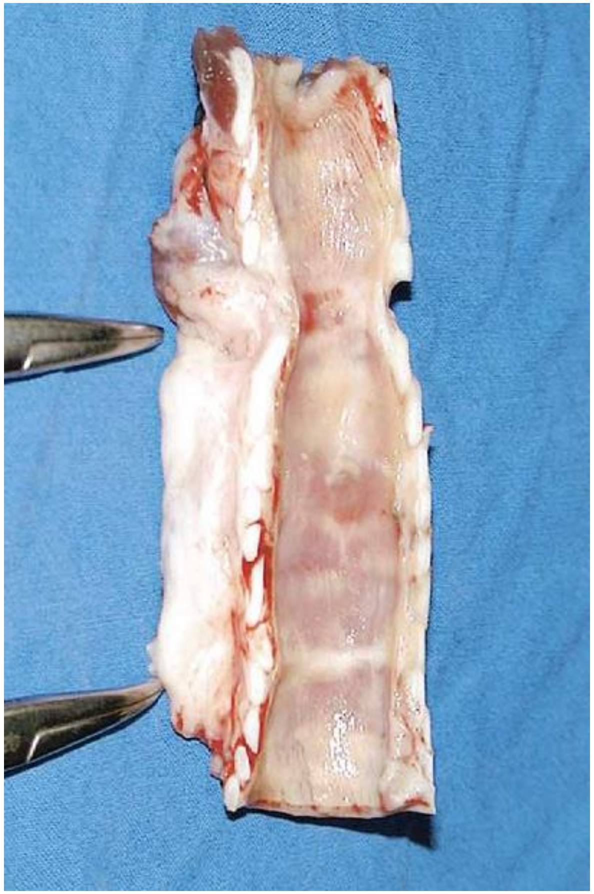
Background. Tracheal reconstruction after extensive resection remains a challenge in thoracic surgery. The goal of this experimental study was to analyze the long-term evolution of tracheal replacement using an autologous aortic graft.

Methods. In 21 sheep, a 5-cm segment of the cervical trachea was replaced by a segment of the descending thoracic aorta that was reconstructed to a prosthetic graft. Because of the airway collapse reported in a previous series, a permanent (n = 13) or temporary (n = 8) stent was systematically placed in the lumen of the graft. Clinical, bronchoscopic, and histologic examinations were performed up to 3 years after implantation.

Results. All animals survived the operation with no paraplegia. In the group with a permanent stent, three complications occurred: one stent displacement, one laryngeal edema, and one infection. Stent removal was tolerated after 6 months in the group with a temporary stent. Histologic examination showed a progressive transformation of the arterial segment into first extensive inflammatory tissue with a squamous epithelium, and after 6 to 36 months well-differentiated tracheal tissue including a continuous mucociliary epithelium and regular rings of newly formed cartilage.

Conclusions. An autologous aortic graft used as a substitute for extensive tracheal replacement in sheep remained functional for periods up to 3 years. The progressive transformation of the graft into a structure resembling tracheal tissue seems to be a key factor in long-term patency. The mechanism of this regenerative process and the possibility of using arterial homografts, which would make clinical application easier, remain to be evaluated.

(Ann Thorac Surg 2003;75:1572–8)



Airway Transplantation Using Stented Aortic Matrices
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-Regeneration of epithelium and de novo generation of cartilage: stent removal after 6 months

STEP 3 : FRESH AORTIC ALLOGRAFT

Tracheal Regeneration Following Tracheal Replacement With an Allogenic Aorta

Emmanuel Martinod, MD, PhD, Agathe Seguin, MD, Muriel Holder-Espinasse, MD, Marianne Kambouchner, MD, Martine Duterque-Coquillaud, PhD, Jacques F. Azorin, MD, and Alain F. Carpentier, MD, PhD

Laboratoire d'Etude des Greffes et Prothèses Cardiaques, Hôpital Broussais, Université Paris 6; Service de Chirurgie Thoracique et Vasculaire, Hôpital Avicenne, Université Paris 13; Service d'Anatomo-Pathologie, Hôpital Avicenne, Université Paris 13, Paris; and Institut de Biologie, Lille, France

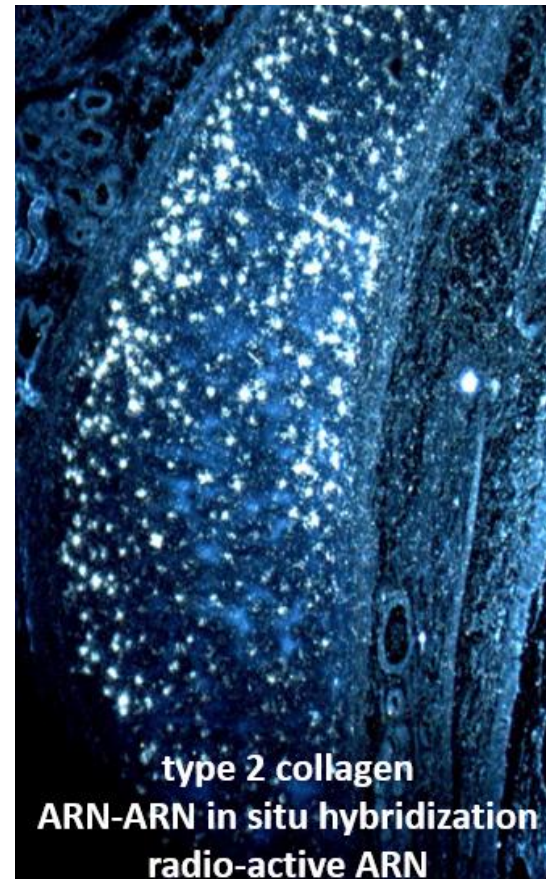
Background. Tracheal replacement remains an unsolved surgical problem. Attempts to use tracheal substitutes have failed to achieve reliable results. In this study, tracheal regeneration was obtained after tracheal replacement with an allogenic aorta.

Methods. Twenty female sheep underwent a 8-cm tracheal replacement with a fresh aortic allograft. In the six last animals, aortic grafts came from male sheep. A stent prevented airway collapse. No immunosuppressive therapy was used. Aortic segments were retrieved at regular intervals up to 16 months. A polymerase chain reaction for the SRY gene was performed in specimens with aortic grafts from male sheep.

Results. All animals but one survived the operation without complications. Clearly identified between the suture lines, the aortic segments were completely transformed into a tracheal structure. Histology showed initially an inflammatory reaction with proliferation of a squamous epithelium followed by mucociliary epithelium and newly formed cartilage rings. SRY gene was not found in newly formed cartilage rings showing that the regeneration originated from recipient cells.

Conclusions. This study presents a new type of tissue regeneration and brings hopes to the treatment of extensive tracheal lesions.

(Ann Thorac Surg 2005;79:942–9)



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-Regeneration of epithelium and de novo generation of cartilage: stent removal after 6 months

STEP 4 : FRESH AORTIC ALLOGRAFT - CARINA

Carinal Replacement With an Aortic Allograft

Agathe Seguin, MD, Emmanuel Martinod, MD, PhD, Marianne Kambouchner, MD, Gabriella O. Campo, MD, Pascale Dhote, MD, Patrick Bruneval, MD, Jacques F. Azorin, MD, and Alain Carpentier, MD, PhD

Laboratoire d'Etude des Greffes et Prothèses Cardiaques, Hôpital Broussais, Paris, Service de Chirurgie Thoracique et Vasculaire, Hôpital Avicenne, Paris, Service d'Anatomo-Pathologie, Hôpital Avicenne, Paris, and Service d'Anatomo-Pathologie, Hôpital Européen George Pompidou, Paris, France

Background. Carinal replacement after extensive resection remains a tremendous challenge in thoracic surgery. In previous studies, we demonstrated that an aortic graft could be a valuable tracheal substitute. The goal of this new study was to evaluate the reconstruction of the carina using a stent supported bifurcated aortic allograft.

Methods. In 15 sheep the replacement of the tracheobronchial bifurcation with an aortic allograft was performed under cardiopulmonary bypass. A temporary stent prevented airway collapse. No immunosuppression was used. Aortic segments were retrieved at regular intervals up to 24 months after implantation.

Results. All animals survived the initial aortic allograft operation. Six animals died postoperatively (1 of graft necrosis, 2 of pneumonia, and 3 of bronchial fistula). The remaining 9 animals were in good condition until they were euthanized. Stent removal was tolerated after 9 months in 3 animals. Progressive transformation of the arterial graft initially into extensive inflammatory tissue, and after 3 to 6 months into a tracheal tissue comprising a well-differentiated epithelium and cartilage was confirmed by histology.

Conclusions. This study showed that regeneration of a functional tissue can be obtained after replacement of the carina with an aortic allograft. The origin and mechanisms of this regenerative process remains to be discovered. These results represent an important hope for the reconstruction of the carina after extensive resection, especially for cancer lesions. In human application, the systemic use of omentoplasty or myoplasty should further reduce its risk of complication.

(Ann Thorac Surg 2006;81:1068–75)

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STEP 5 : CRYOPRESERVED AORTIC ALLOGRAFT

Tracheal Replacement With Cryopreserved, Decellularized, or Glutaraldehyde-Treated Aortic Allografts

Agathe Seguin, MD, Dana Radu, MD, Muriel Holder-Espinasse, MD, PhD, Patrick Bruneval, MD, Anne Fialaire-Legendre, MD, Martine Duterque-Coquillaud, PhD, Alain Carpentier, MD, PhD,* and Emmanuel Martinod, MD, PhD*

Laboratoire de Recherches Biochirurgicales, Fondation Alain Carpentier, Université Paris V, Paris, Assistance Publique-Hôpitaux de Paris, Hôpital Avicenne, Département de Chirurgie Thoracique et Vasculaire, Université Paris XIII, Faculté de Médecine SMH, Bobigny, Institut de Biologie, Lille, Assistance Publique-Hôpitaux de Paris, Hôpital Européen George Pompidou, Département d'Anatomopathologie, Université Paris V, Faculté de Médecine, Paris, and Assistance Publique-Hôpitaux de Paris, Hôpital Henri Mondor, EFS Ile de France, Banque de Tissus, Créteil, France

Background. Seven years of experimental research provided a valuable tracheal substitute, the aortic allograft, which can promote the regeneration of epithelium and cartilage. In human application, both fresh and preserved aortic allografts could be used. The optimal method of aortic allograft preservation remains to be evaluated. This study assessed the use of cryopreserved, decellularized, or glutaraldehyde-treated aortic allografts as tracheal substitutes.

Methods. Twenty-two sheep underwent tracheal replacement using cryopreserved (n = 10), decellularized (n = 7) or glutaraldehyde-treated (n = 5) allografts, supported by a temporary stent to prevent airway collapse. Aortic segments were retrieved at regular intervals up to 12 months after implantation to analyze the regenerative process.

Results. All animals survived the operation. Major complications such as infection, stent migration, or obstruction were predominantly encountered in the decellularized group. The lack of major inflammatory response within the aortic graft observed in the glutaraldehyde group was associated with the absence of tracheal regeneration. Histologic examinations showed a progressive transformation of the aorta into a tracheal tissue comprising respiratory epithelium and cartilage only in the cryopreserved group.

Conclusions. This study demonstrated that regeneration of a functional tissue could be obtained after tracheal replacement with a cryopreserved aortic allograft. The regenerative process followed the same pattern as previously described for fresh allografts. Cryopreserved aortic allografts present major advantages: availability in tissue banks, permanent storage, and no need for immunosuppression. This offers a new field of perspectives for clinical application in patients with extensive tracheal cancer.

(Ann Thorac Surg 2009;87:861–8)

Table 2. Complications, Follow-up, and Histologic Examinations

Group, Animal No.	Complications	State	Follow-Up, Mon	Patency	Epithelium	Cartilage
Group 1						
Cryopreserved at –80°C						
1	...	Sacrificed	1	100%	Squamous, interrupted	0
2	Thymic abscess	Dead	2	100%	Mixed, interrupted	0
3	...	Sacrificed	6	100%	Mucociliary, continuous	+
4	...	Sacrificed	6	100%	Mucociliary, continuous	+
5	...	Sacrificed	12	100%	Mucociliary, continuous	++
At –150°C						
6	...	Sacrificed	1	100%	Squamous, interrupted	0
7	Stent migration	Dead	2.5	Stenosis > 70%	Mixed, interrupted	0
8	...	Sacrificed	3	100%	Mixed, continuous	+/–
9	...	Sacrificed	3	100%	Mixed, continuous	+/–
10	...	Sacrificed	6	100%	Mucociliary, continuous	+
Group 2: Decellularized						
11	...	Sacrificed	1	100%	Squamous, interrupted	0
12	Local infection	Dead	2	100%	Ulceration	0
13	Local infection	Dead	2	100%	Ulceration	0
14	Local infection	Dead	2	100%	Ulceration	0
15	Unknown	Dead	4	100%	Squamous, interrupted	0
16	Stent obstruction	Dead	5	0%	Mixed, interrupted	0
17	...	Sacrificed	12	100%	Metaplastic	0
Group 3: Glutaraldehyde treatment						
18	...	Sacrificed	1	100%	Squamous, interrupted	0
19	Stent migration	Dead	2.5	Stenosis > 70%	Squamous, interrupted	0
20	Stent migration	Dead	2.5	Stenosis > 70%	Squamous, interrupted	0
21	...	Sacrificed	3	100%	Mixed, interrupted	+/–
22	...	Sacrificed	6	100%	Mixed, interrupted	+/–

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-Regeneration of epithelium and de novo generation of cartilage: stent removal after 6 months

STEP 6 : TRACHEAL REGENERATION

Tracheal regeneration: Evidence of bone marrow mesenchymal stem cell involvement

Agathe Seguin, MD, PhD,[a,b,c] Sonia Baccari, MD,[a,c] Muriel Holder-Espinasse, MD, PhD,[d] Patrick Bruneval, MD,[e] Alain Carpentier, MD,[a] Doris A. Taylor, PhD,[c] and Emmanuel Martinod, MD, PhD[a,b]

Objectives: Recent advances in airway transplantation have shown the ability of ex vivo or in vivo tracheal regeneration with bioengineered conduits or biological substitutes, respectively. Previously, we established a process of in vivo–guided tracheal regeneration using vascular allografts as a biological scaffold. We theorized that tracheal healing was the consequence of a mixed phenomenon associating tracheal contraction and regeneration. The aim of the present study was to determine the role that bone marrow stem cells play in that regenerative process.

Methods: Three groups of 12 rabbits underwent a gender-mismatched aortic graft transplantation after tracheal resection. The first group received no cells (control group), the second group had previously received autologous green fluorescent protein–labeled mesenchymal stem cell transplantation, and the third group received 3 labeled mesenchymal stem cell injections on postoperative days 0, 10, and 21.

Results: The clinical results were impaired by stent complications (obstruction or migration), but no anastomotic leakage, dehiscence, or stenosis was observed. The rabbits were killed, and the trachea was excised for analysis at 1 to 18 months after tracheal replacement. In all 3 groups, microscopic examination showed an integrated aortic graft lined by metaplastic epithelium. By 12 months, immature cartilage was detected among disorganized elastic fibers. Positive SRY gene detection served as evidence for engraftment of cells derived from the male recipient. EF-green fluorescent protein detection showed bone marrow–derived mesenchymal stem cell involvement.

Conclusions: The results of the present study imply a role for bone marrow stem cells in tracheal regeneration after aortic allografting. Studies are necessary to identify the local and systemic factors stimulating that regenerative process. (J Thorac Cardiovasc Surg 2012;■:1-8)

FIGURE E2. Macroscopic examination at 15 months from injection showing moderate retraction and integrated graft. *Arrows* indicate graft limits.

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STEP 7 : BRONCHIAL REPLACEMENT

Bronchial Replacement With Arterial Allografts

Dana M. Radu, MD, Agathe Seguin, MD, Patrick Bruneval, MD, PhD, Anne Fialaire Legendre, MD, Alain Carpentier, MD, PhD,* and Emmanuel Martinod, MD, PhD*

Département de Chirurgie Thoracique et Vasculaire, Assistance Publique-Hôpitaux de Paris, Hôpital Avicenne, Université Paris XIII, Faculté de Medecine SMBH, Bobigny; Université Paris Descartes, EA Laboratoire de Recherches Biochirurgicales, Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Paris; Département d'Anatomopathologie, Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Université Paris Descartes, Faculté de Médecine, Paris; and Etablissement Français du Sang Ile de France, Banque de Tissus, Assistance Publique-Hôpitaux de Paris, Hôpital Henri Mondor, Créteil, France

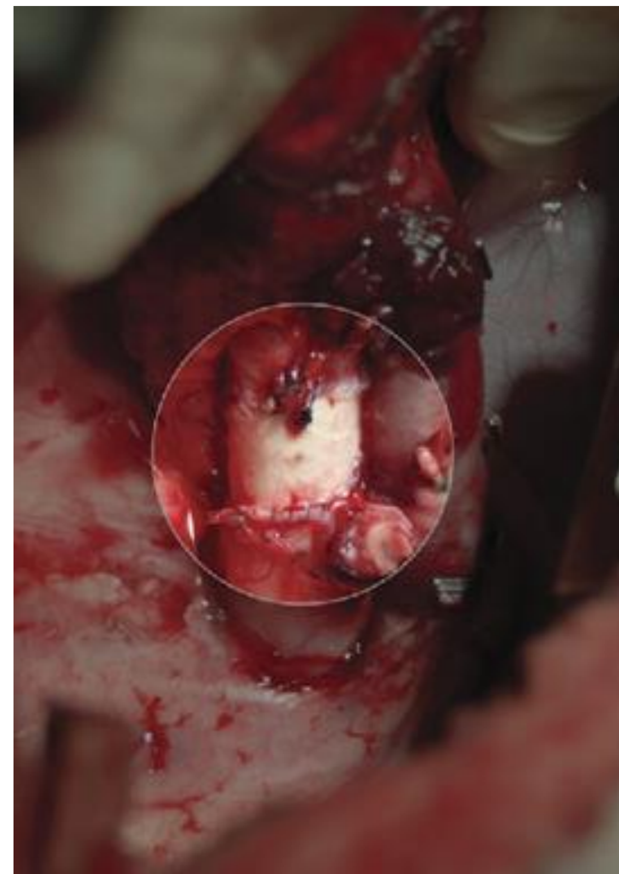
Background. Pneumonectomy is well known for a high risk of postoperative death. The alternative, sleeve lobectomy, is sometimes technically inaccessible, and is associated with locoregional recurrence. In certain situations, the use of a bronchial substitute would allow longer bronchial resections with better security margins. Previous experiments demonstrated that aortic grafts are valuable tracheal and carinal substitutes. The present study evaluated bronchial replacement with arterial allografts.

Methods. Fifteen female sheep underwent a left bilobectomy with replacement of the bronchus intermedius with arterial allografts: 5 received a fresh graft (group 1) and 10 received cryopreserved (group 2). A bronchial silicone stent was used to confer rigidity. Evaluation was conducted on clinical and histologic criteria at regular intervals up to 18 months.

Results. There were no perioperative deaths. Atelectasis, the only early postoperative complication (n = 2), was successfully treated by fiberscopic aspiration. The late postoperative period was uneventful in 12 sheep. Complications included 1 bronchopneumonia, 1 pulmonary abscess, and 1 distortion of the bronchial stent. Fiberscopic examination revealed 3 sheep with granuloma formation. The bronchial stent was removed in 3 sheep, 1 at 9 months and 2 at 12 months, without clinical complications or stenosis of the graft. Histologic analysis showed regeneration of new bronchial tissue, comprising epithelium and cartilage.

Conclusions. This study confirmed that an arterial allograft could be a valuable bronchial substitute. The use of a bronchial substitute offers new perspectives in surgical resection of lung cancer because it would avoid pneumonectomy in some patients.

(Ann Thorac Surg 2010;90:252–8)



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CHEST Original Research
INTERVENTIONAL PULMONOLOGY

Tracheal Replacement by Allogenic Aorta in the Pig*

Sophie Jaillard, MD, PhD; Muriel Holder-Espinasse, MD, PhD; Thomas Hubert, DVM, PhD; Marie-Christine Copin, MD, PhD; Martine Duterque-Coquillaud, PhD; Alain Wurtz, MD; and Charles-Hugo Marquette, MD, PhD

CHEST 2006; 130:1397–1404,

FRESH

CONFIRMED...

CHEST Original Research
NEOPLASTIC DISEASE

Tracheal Replacement With Cryopreserved Allogenic Aorta

Demosthènes Makris, MD, PhD; Muriel Holder-Espinasse, MD, PhD; Alain Wurtz, MD; Agathe Seguin, MD; Thomas Hubert, DVM, PhD; Sophie Jaillard, MD, PhD; Marie Christine Copin, MD, PhD; Ramadan Jashari, MD; Martine Duterque-Coquillaud, PhD; Emmanuel Martinod, MD, PhD; and Charles-Hugo Marquette, MD, PhD

CHEST 2010; 137(1):60–67

CRYOPRESERVED

CH Marquette and coll.

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-Regeneration of epithelium and de novo generation of cartilage: stent removal after 6 months

… OR DEBATED

Tracheal Replacement With a Silicone-Stented, Fresh Aortic Allograft in Sheep

Hisashi Tsukada, MD, PhD, Armin Ernst, MD, Sidhu Gangadharan, MD, Simon Ashiku, MD, Robert Garland, RTT, Diana Litmanovich, MD, and Malcolm DeCamp, MD

Chest Disease Center and Department of Radiology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

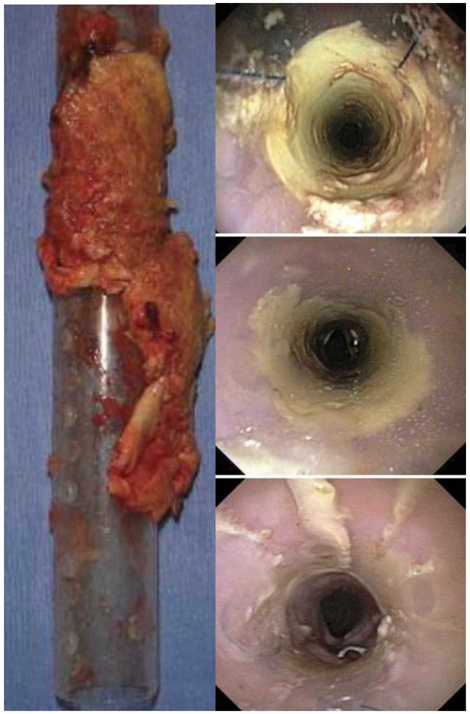
Background. Tracheal tissue regeneration after allogeneic aortic transplants in sheep has been reported. We sought to confirm these findings and elucidate the mechanism of this transformation.

Methods. Ten male sheep underwent cervical tracheal replacement with fresh, descending thoracic aortic allografts, 8 cm long, from female sheep, without postoperative immunosuppressive therapy. A 10-cm silicone stent was placed to prevent airway collapse. Graft evaluations with flexible bronchoscopy and computed tomography were conducted between 2 weeks and 1 year after surgery.

Results. There were no procedural deaths, but 6 animals died or required euthanasia between 12 days and 3 months postoperatively owing to severe tracheitis, cervical lymphadenitis, pneumonia, graft necrosis, stent migration, or airway obstruction after stent removal. The 4 remaining sheep were euthanized as planned at 6 to 12 months after surgery. Harvested tracheas revealed no evidence of graft incorporation into the surrounding tissue, and there was no histologic evidence of any neocartilage within or around the graft at any point. Bronchoscopy revealed marked graft necrosis in the 4 animals surviving to planned euthanasia. In all sheep, computed tomography imaging revealed that the graft was replaced by connective tissue without any signs of cartilage regeneration. Image analysis also indicated profound shortening of the grafted area up to 87.5% at 1 year after implantation, secondary to axial shift of the native trachea.

Conclusions. Fresh aortic allografts appear to be unsuitable for primary tracheal replacement. However, the observed graft shortening may allow for two-staged, end-to-end reconstruction of large tracheal defects with temporary grafting techniques.

(Ann Thorac Surg 2010;89:253–8)



Airway Transplantation Using Stented Aortic Matrices
-Biological studies : regeneration from recipient cells
-Epithelium : native airways / Cartilage : involvement of bone marrow mesenchymal stem cells
-Aortic matrices : release of cytokines and growth factors by remaining viable cells
-Favorable results led to the first human applications

DID THE CARTILAGE REGENERATION COME FROM AORTIC OR RECIPIENT CELLS ?


XY

→


XX

Allograft study (N = 20) : 6 last animals, replacement of XX trachea with XY aortic allograft

Is the Y chromosome present in the newly formed cartilage ?
PCR technique on SRY genes (Y chromosome) and IGF1 (control)

Martinod E et al. Tracheal regeneration following tracheal replacement with an allogenic aorta. Ann Thorac Surg 2005;79:942– 8.

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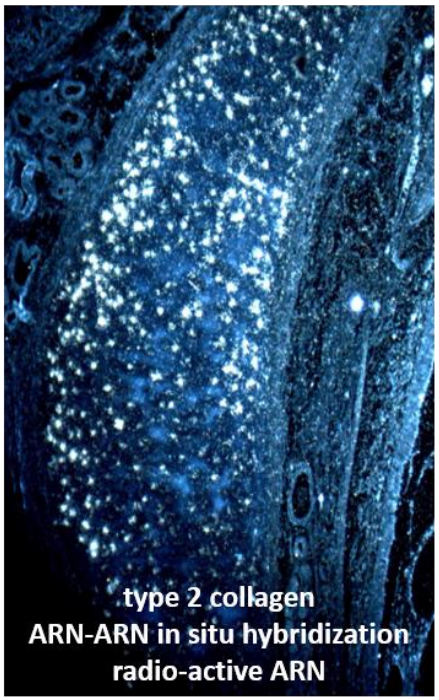

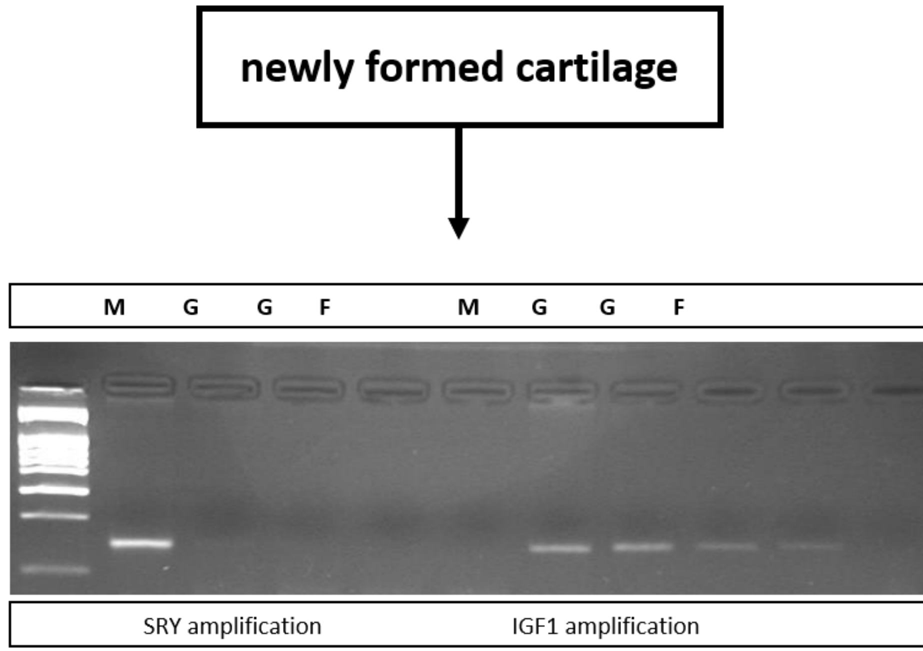

THE REGENERATED CARTILAGE CAME FROM RECIPIENT CELLS

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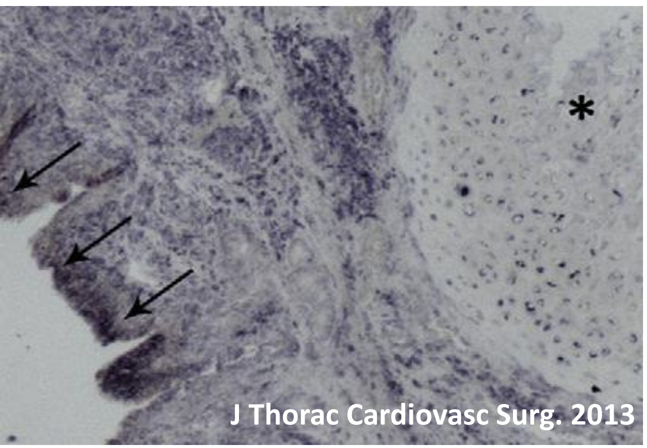
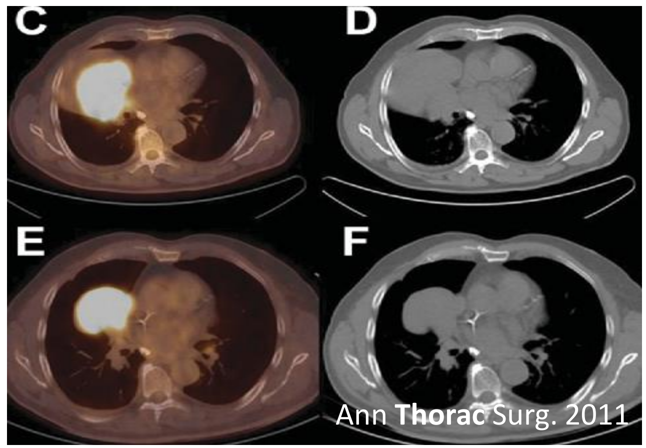
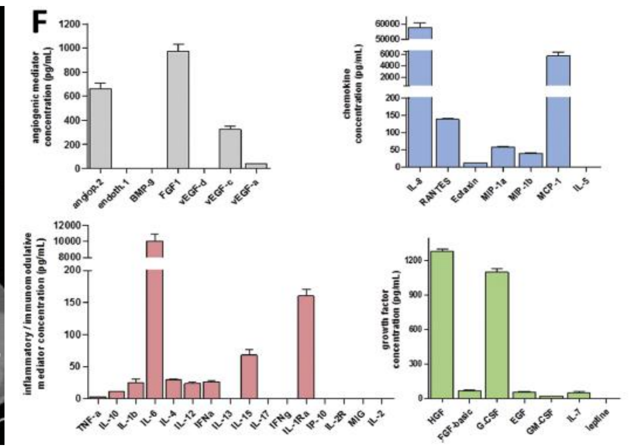
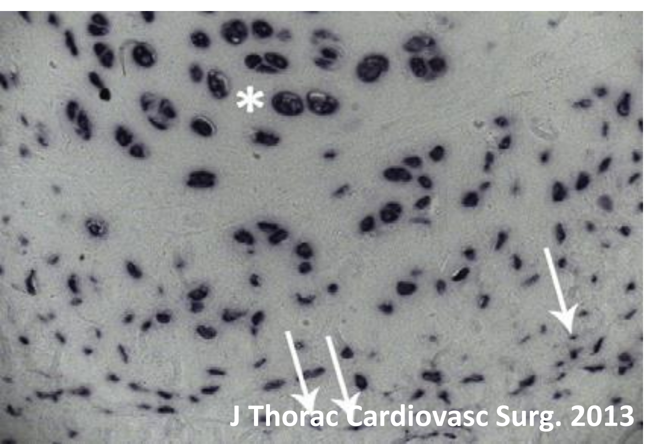


J Thorac Cardiovasc Surg. 2013

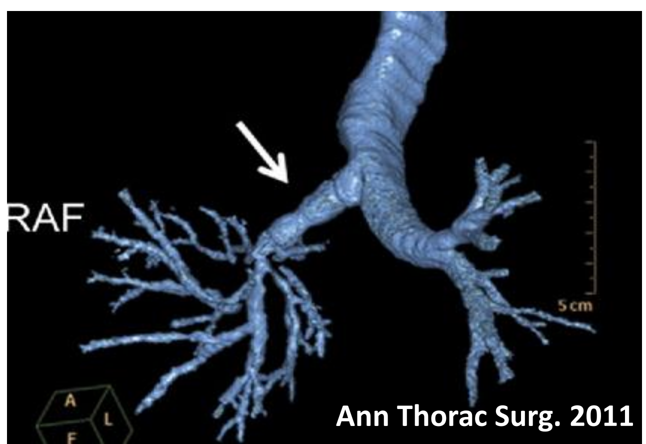


Ann Thorac Surg. 2011

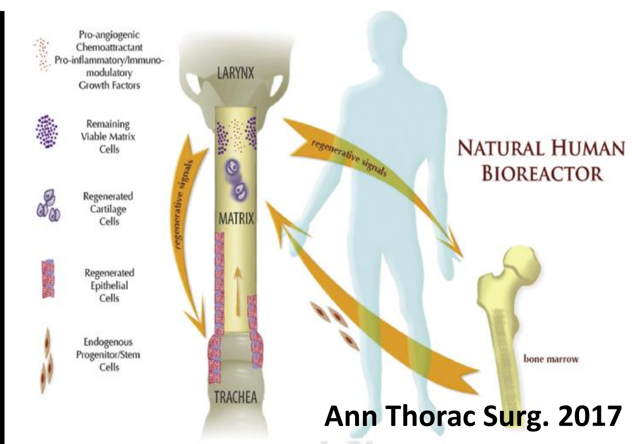




J Thorac Cardiovasc Surg. 2013



Ann Thorac Surg. 2011



Ann Thorac Surg. 2017

Feasibility of Airway Transplantation Using a Bioengineered Stented Aortic Allograft

JAMA. 2018 Jun 5;319(21):2212-2222

This prospective study was designed to evaluate the feasibility of airway bioengineering using stented cryopreserved aortic allografts as biological matrices

Methods

Study Design

Sponsor: DRCD, Clinical Research Unit (E. Vicaut)

French National Institutional Ethical Review Board Approval

Patients

with:

-major malignant or benign lesions of the trachea, carina and bronchi untreated with conventional therapeutic approaches,

-proximal lung tumors requiring pneumonectomies

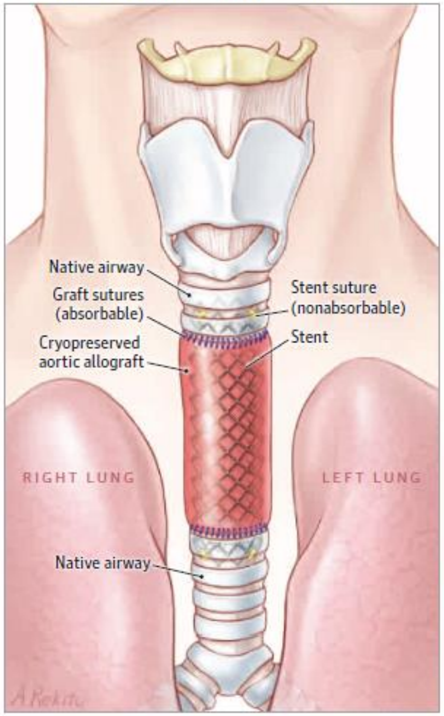
TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01331863

Methods

Treatment

Radical resection of the lesions was performed using standard surgical techniques
A conventional solution for airway reconstruction was preferred when feasible

A Airway transplantation using stented aortic matrix



Airway reconstruction

Human cryopreserved (−80°C) aortic allograft
from a certified tissue bank, **APHP EFS Ile de France Banque des Tissus Créteil**
not matched by the ABO and leukocyte antigen systems

Stent (custom-made) to prevent airway collapse
-fully covered nitinol stent (Silmet, Novatech)
-or a silicone stent (Tracheobronxane Dumon, Novatech)

Local muscle flap to promote neovascularization
and prevent fistulization

No immunosuppressive therapy

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

JAMA. 2018 Jun 5;319(21):2212-2222

Methods

Follow-up and Assessment of Outcomes

Primary outcome: 90-day mortality

Secondary outcome: 90-day morbidity

After 90 days: all patients followed up for long-term mortality and morbidity outcomes
Last follow-up: November 2, 2017

Biopsy specimens from cryopreserved aortic allografts after stent removal
-at 15 months in a woman (patient 2) who received an allograft from a male donor
-at 39 months in a man (patient 4) who received an allograft from a female donor

Tissues identified as neoepithelium, neocartilage, and granuloma isolated and used for histological studies

Biopsy specimens from patient 2 were used for engraftment (chimerism) studies

Feasibility of Airway Transplantation Using a Bioengineered Stented Aortic Allograft

JAMA. 2018 Jun 5;319(21):2212-2222

Results

Patients

Oct 2009 - Feb 2017: 20 patients

13 M - 7 F, mean age of 54.9 years

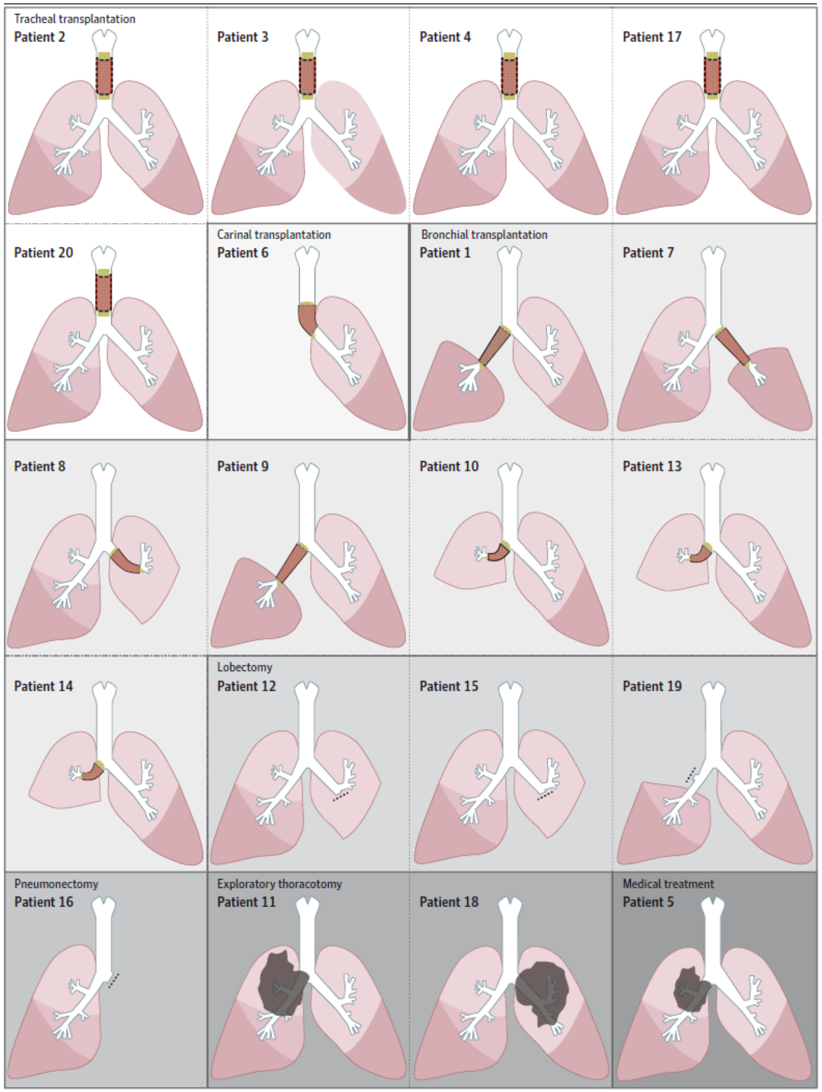
5 patients :
-extensive benign (n = 3) or malignant (n = 2) tracheal lesions for which previous treatment had failed

1 patient:
-carcinoid tumor extending to the distal trachea, carina, and main right bronchus

14 patients:
to avoid a pneumonectomy
-non small cell lung cancer (n = 11)
-carcinoid tumor (n = 2)
-rhabdomyosarcoma (n = 1)

Procedures

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



Lobectomy or bilobectomy was performed in all cases of bronchial transplantation. In patients 12, 15, 16, and 19, dashed lines indicate the bronchial suture. In patients 5, 11, and 18, transparent gray irregular shapes represent proximal lung tumors that could not be resected.

Feasibility of Airway Transplantation Using a Bioengineered Stented Aortic Allograft

JAMA. 2018 Jun 5;319(21):2212-2222

Results

Primary Outcome

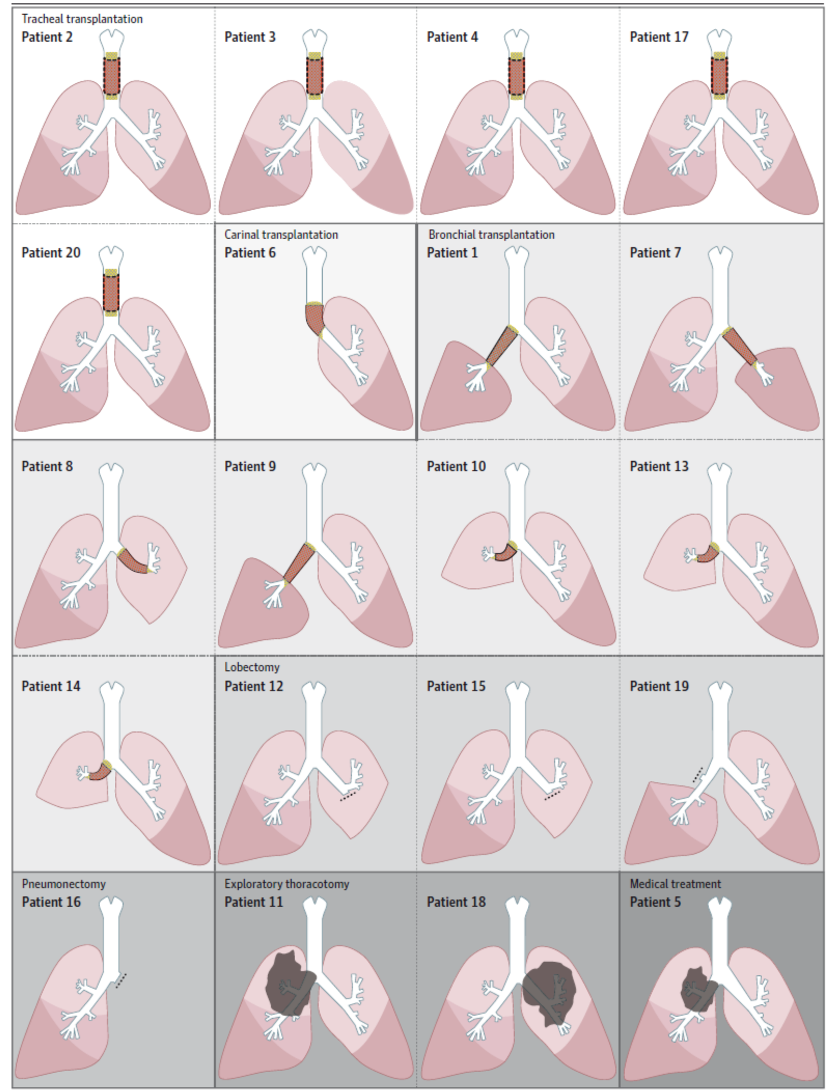
- -13 patients: airway transplantation
- -7 patients: standardized approach
- -90-day mortality = 7.7%
- -Patient 6 died (major stroke)
- -No mortality associated with tracheal or bronchial transplantation

Secondary Outcomes

- -Among the 13 patients who underwent airway transplantation, major 90-day morbidity in 4 patients (30.8%): laryngeal edema, acute lung edema, acute respiratory distress syndrome, and atrial fibrillation
- -There was no adverse event directly related to the surgical technique

Procedures

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



Lobectomy or bilobectomy was performed in all cases of bronchial transplantation. In patients 12, 15, 16, and 19, dashed lines indicate the bronchial suture. In patients 5, 11, and 18, transparent gray irregular shapes represent proximal lung tumors that could not be resected.

JAMA. 2018 Jun 5;319(21):2212-2222

Results

Long-term Follow-up

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

[a] From the date of the operation.

Stent-related complications (granulomas) in 7 patients : bronchoscopic management
No major complication specifically related to the allograft or the stent
Maximal follow-up of 7 years 1 month: 10 patients (76.9%) alive. Of these 10 patients, 8 (80%) breathed normally through newly formed airways after stent removal

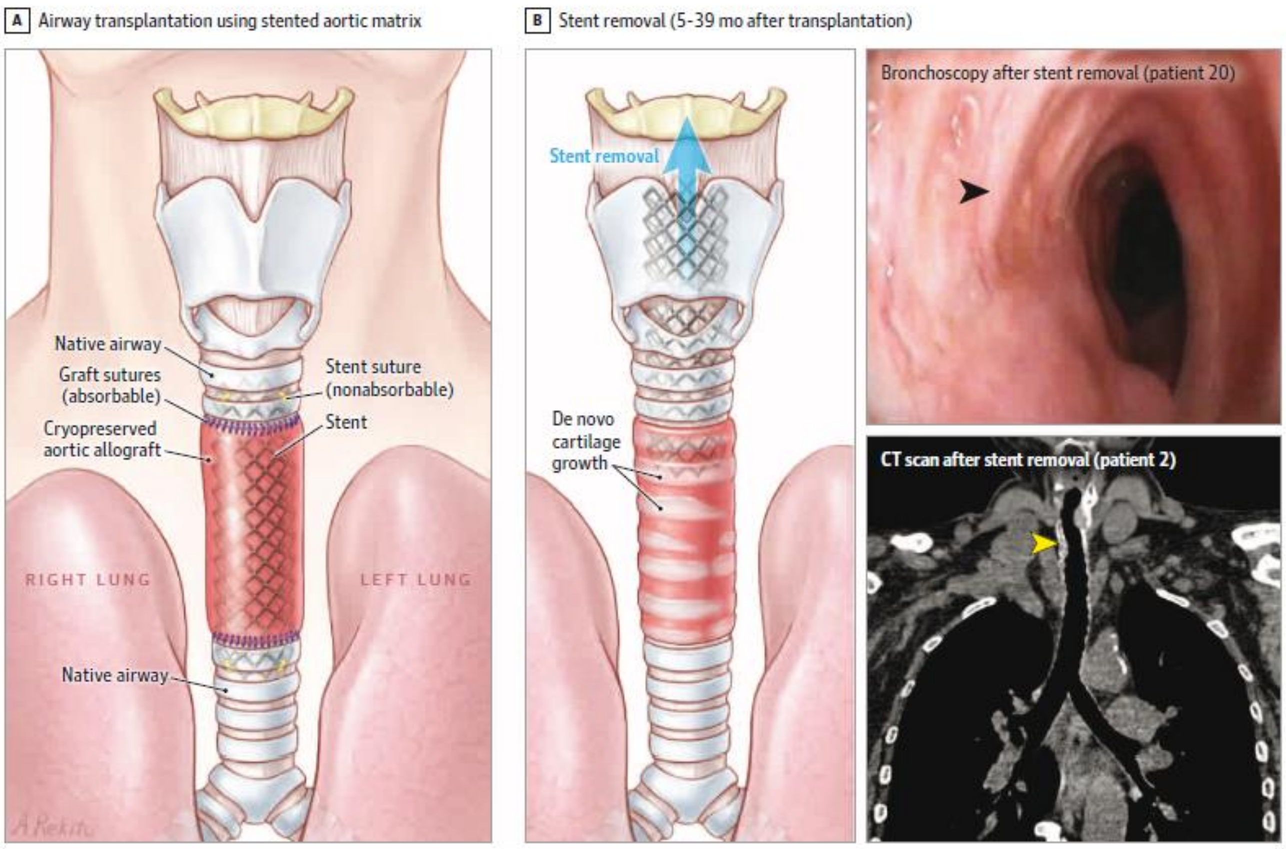
JAMA. 2018 Jun 5;319(21):2212-2222

Results

Long-term Follow-up

Stent removal (n = 9; 69.2%) between months 5 and 39 at a mean of 18.2 months

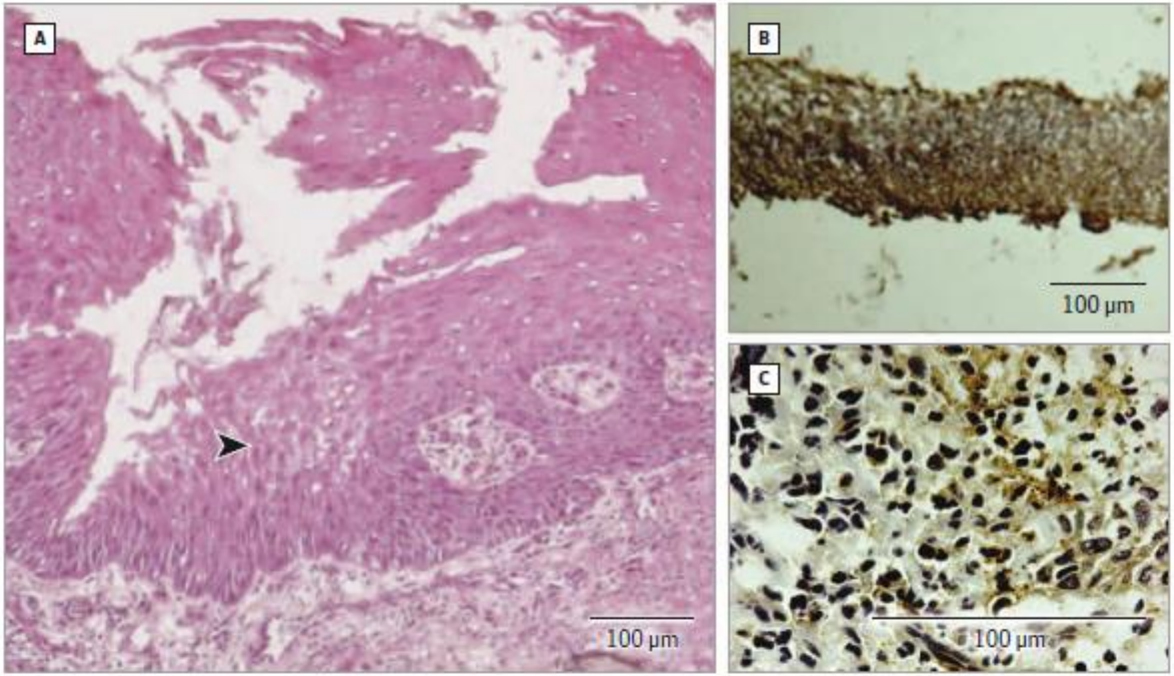
Figure 1. De Novo Generation of Cartilage Within Stented Cryopreserved Aortic Matrices After Surgical Resection of End-Stage Tracheal Lesions or Proximal Lung Tumors



Results

Long-term Follow-up

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



Pathological examination: regeneration of a mixed respiratory epithelium
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

Videobronchoscopy Visualization of De Novo Cartilage Formation After Stent Removal Following Airway Reconstruction Using a Stented Aortic Matrix

JAMA

JAMA Network™

Discussion

Airway bioengineering using stented aortic matrices: feasibility for complex tracheal and bronchial reconstruction

Field of airway transplantation: recent advances have been associated with important scientific and ethical controversies

International Society of Cell Therapy specific recommendations for human airway bioengineering: prospective studies (2014)

Weiss DJ et al. Tracheal bioengineering. Cytotherapy. 2014;16(12):1601-1613.

Pulmonary CELLULAR THERAPY ADVANCEMENTS

Tracheal Bioengineering: The Next Steps

Tuesday, April 22nd, 2014 • 10:45 – 19:30 Le Méridien Etoile Hotel, Paris, France

Daniel J. Weiss, MD, PhD
ISCT Pulmonary Scientific Committee, Chair
Professor of Medicine, University of Vermont, USA

Martin Birchall MA (Hons), MD (Cantab), FRCS, FMedSci
Professor of Laryngology, Royal National Throat, Nose and Ear Hospital
London, UK

Program

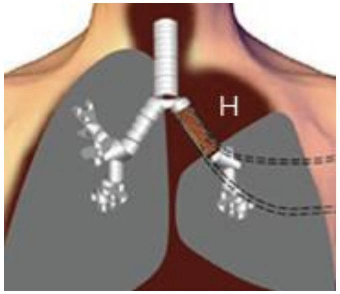
10:45 – 10:50	**WELCOME, AIMS, PARAMETERS** ***Dan Weiss,*** ISCT Pulmonary Scientific Committee, Chair
10:50 – 11:05	**Biomaterials for Tracheal Tissue Engineering** *David Williams*
11:05 – 13:05	**Translational Science** *(15 minute summaries of clinical translational progress by each group, finishing with a list of three major unanswered questions each that highlight barriers to progress, 5 minutes for questions), in alphabetical order by institution:* Karolinska — *Philipp Jungebluth* Leuven — *Pierre Delaere* NEOtrachea EU Consortium — *Alex Seifalian* Paris — *Emmanuel Martinod* Toronto — *Tom Waddell* UCL — *Martin Birchall*

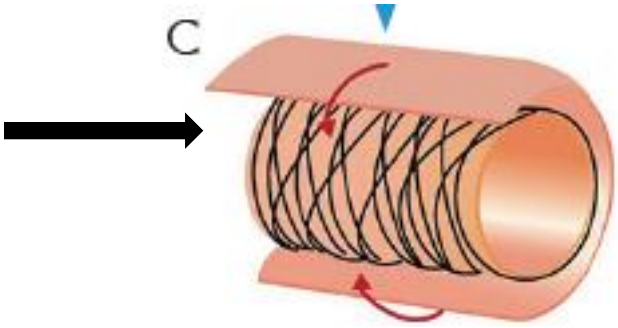
Discussion

90-day mortality rate : low (7.7%) and associated with carinal transplantation (n=1) as reported by some other groups (16,6%) Fabre D et al. Successful tracheal replacement in humans using autologous tissues. *Ann Thorac Surg. 2013;96(4):1146-1155.*

Tracheal transplantation (n = 5)
90-day mortality rate = 0% in contrast with some retrospective reports Teixeira da Silva JA. Ethical perspectives and ramifications of the Paolo Macchiarini case. *Indian J Med Ethics. 2017;2(4):270-275.*

Bronchial transplantation to avoid a high-risk pneumonectomy (n=7)
90-day mortality rate = 0%
In contrast with mortality after pneumonectomy
Interest of bronchial transplantation Tan Q, Liu R, Chen X, et al. Clinic application of tissue engineered bronchus for lung cancer treatment. *J Thorac Dis. 2017;9(1):22-29.*





Feasibility of Airway Transplantation Using a Bioengineered Stented Aortic Allograft

JAMA. 2018 Jun 5;319(21):2212-2222

Discussion

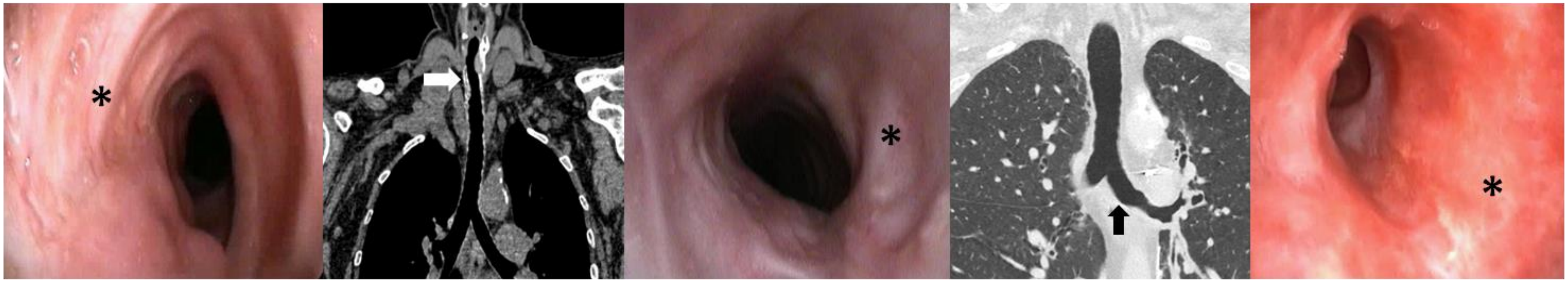
Positive long-term results:

-no death related to the use of stented cryopreserved aortic allografts

-stent removal feasible in the majority of patients as observed in preclinical studies

-majority of patients: breathing and speaking normally without a tracheostomy or stent

-postoperative examinations did not detect a definitive malacia of the cryopreserved aortic allografts after stent removal

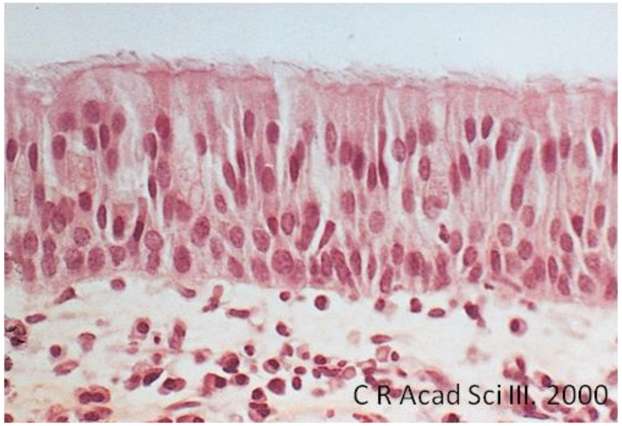


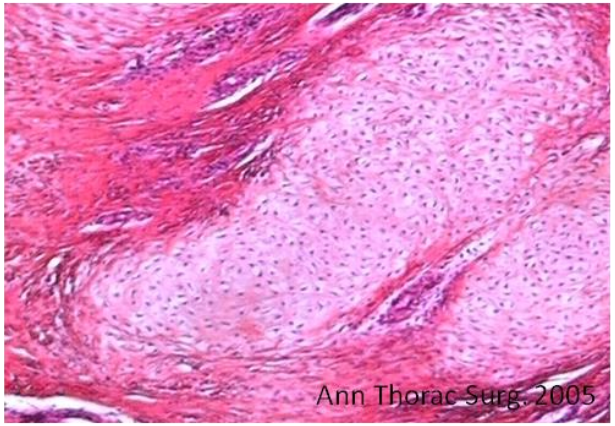
Discussion

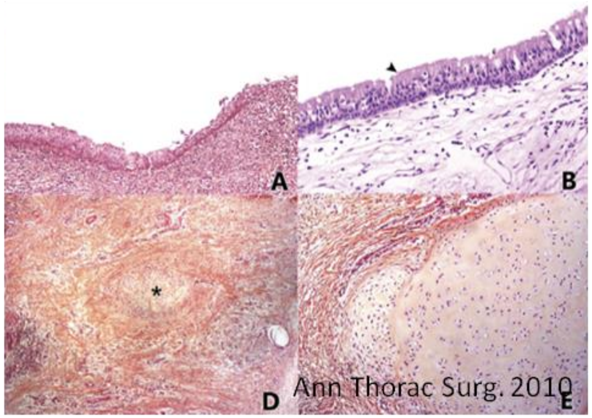
The present study confirmed prior biological observations:

Regeneration of a mixed respiratory epithelium:
Epithelial cells have gradually repopulated the allograft lumen by direct migration and expansion from adjacent native airways (as observed after epithelium destruction)

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



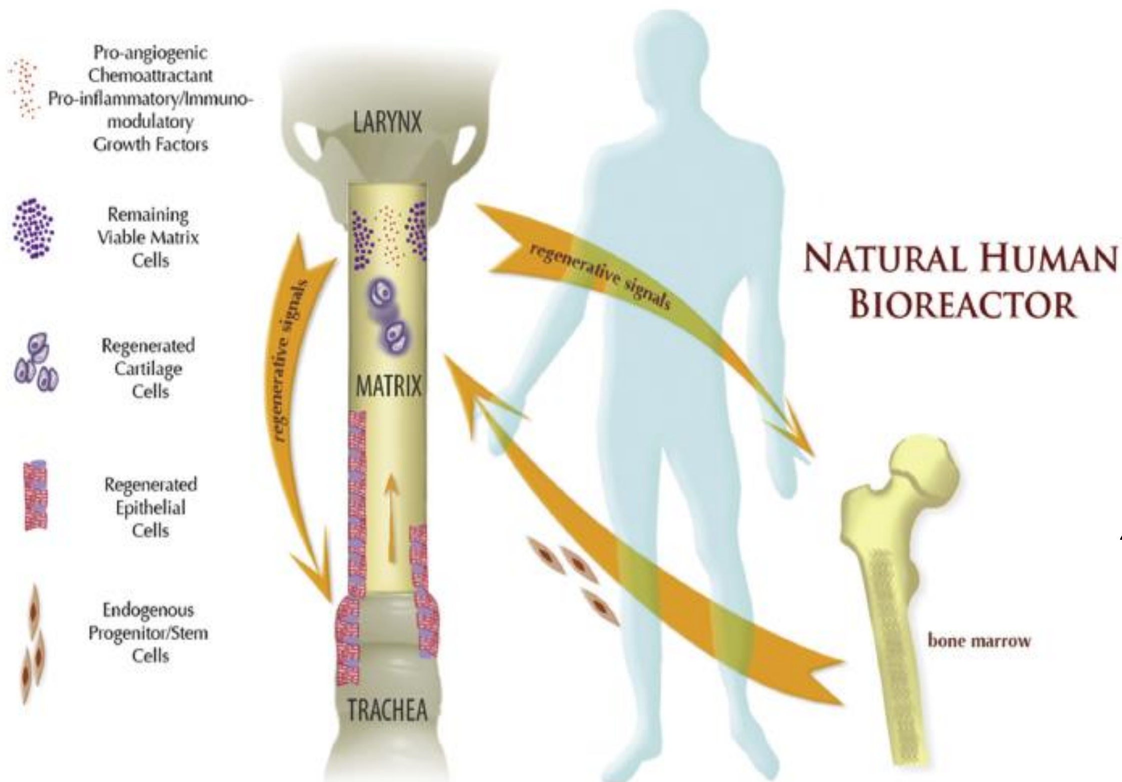




Discussion

Main hypothesis: this phenomenon promoted progenitor or stem cell homing followed by de novo generation of cartilage

Human body: used as a natural bioreactor, allowed in vivo airway tissue engineering

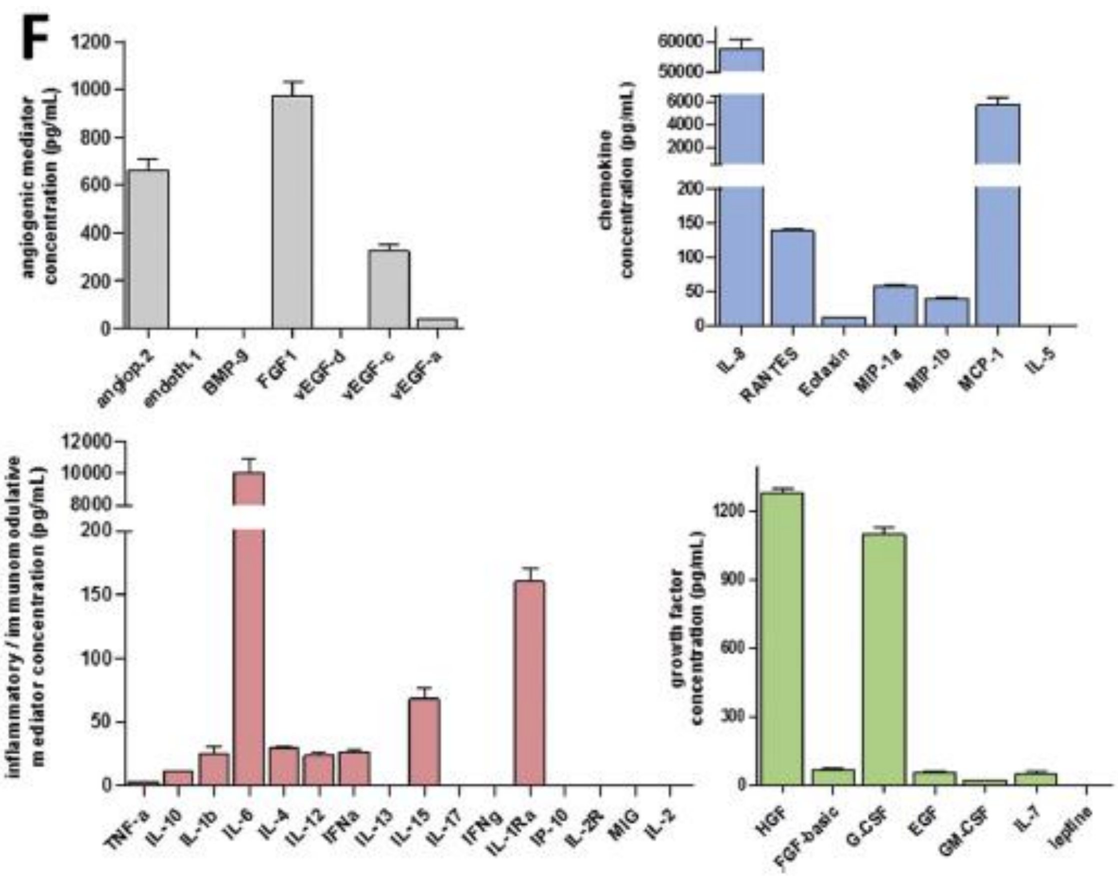


Martinod E et al.
In vivo tissue engineering of human airways.
Ann Thorac Surg. 2017;103(5):1631-1640.

Discussion

Aortic matrices played a significant role by the release of proangiogenic, chemoattractant, proinflammatory and immunomodulatory cytokines, and growth factors

F



Martinod E et al.
In vivo tissue engineering of human airways.
Ann Thorac Surg. 2017;103(5):1631-1640.

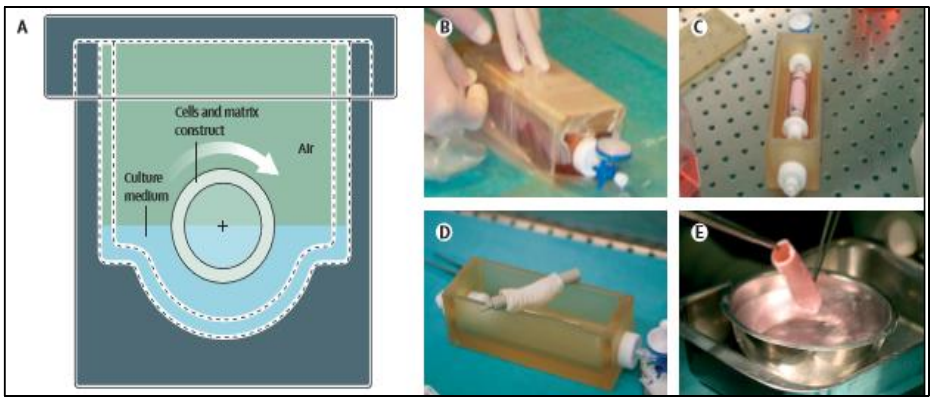
Feasibility of Airway Transplantation Using a Bioengineered Stented Aortic Allograft

JAMA. 2018 Jun 5;319(21):2212-2222

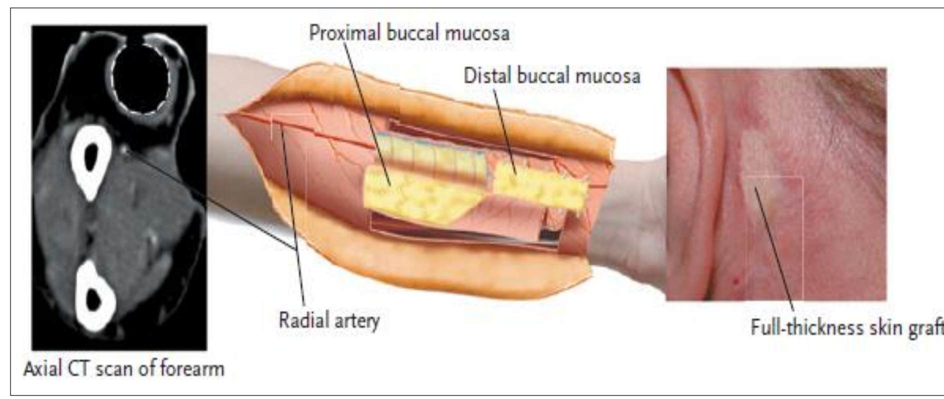
Discussion

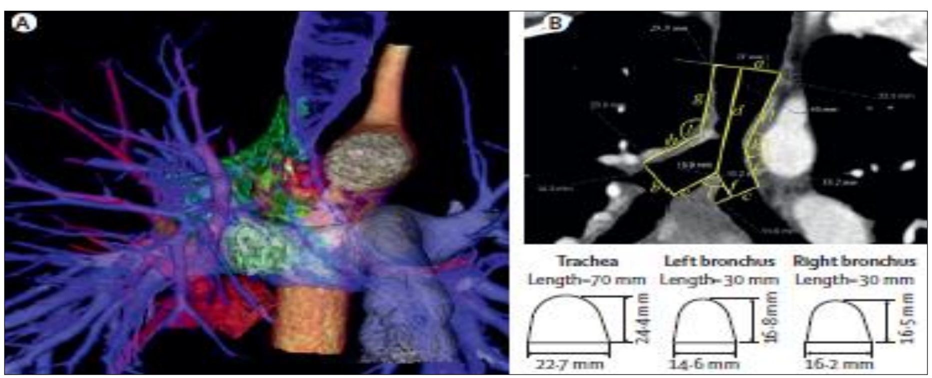
Compared with other techniques, the present solution did not require the use of decellularized cadaveric tracheal allografts, recipient cells, artificial bioreactors, or immunosuppressive treatment

EUROPEAN GROUP Lancet. 2008;372:2023-30

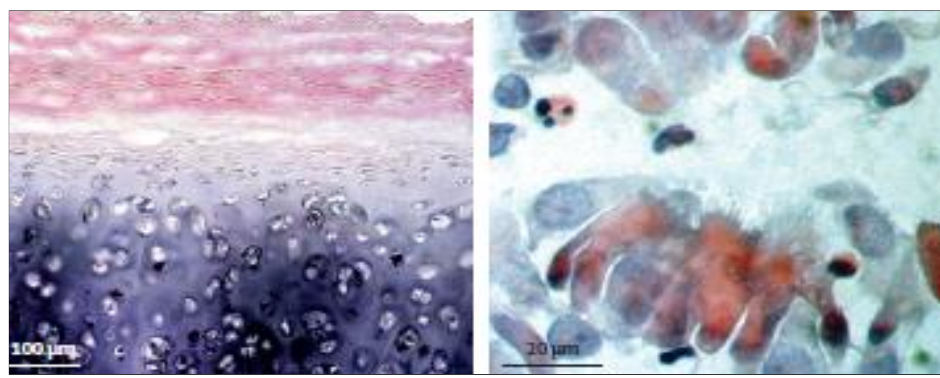


LEUVEN GROUP (DELAERE) N Engl J Med. 2010;362:138-45





MACCHIARINI GROUP Lancet. 2011;378:1997-2004 RETRACTED



LONDON GROUP (ELLIOTT, BIRCHALL) Lancet. 2012;380:994-1000

Feasibility of Airway Transplantation Using a Bioengineered Stented Aortic Allograft

JAMA. 2018 Jun 5;319(21):2212-2222

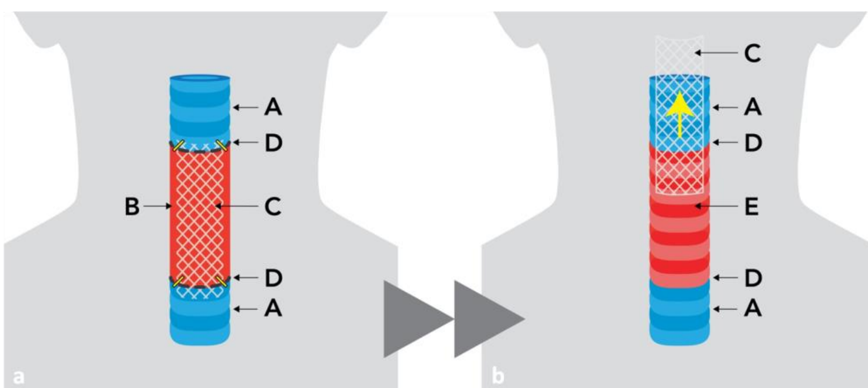
Discussion

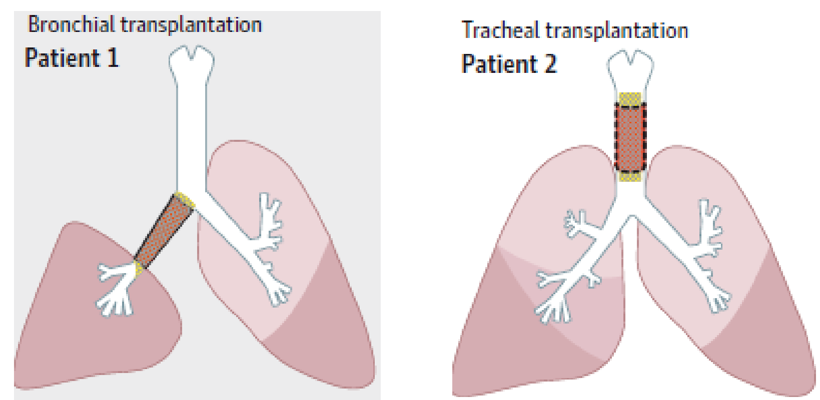
Areas for additional research include

-the possibility to accelerate de novo generation of cartilage for early stent removal;

-the study of mechanisms of airway regeneration within cryopreserved aortic matrices;

-the development of clinical applications using multicenter randomized clinical trials 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.





Feasibility of Airway Transplantation Using a Bioengineered Stented Aortic Allograft

JAMA. 2018 Jun 5;319(21):2212-2222

EDITORIAL

Has Reconstruction of the Central Airways Been Transformed? From Aorta to Trachea

Valerie W. Rusch, MD

in the creation of custom airway stents. Overall, this approach provides an elegant solution to challenges that have long bedeviled the field of tracheal surgery. For some patients with cancer, this approach may preserve lung function and quality of life by avoiding pneumonectomy while permitting an oncologically sound operation.[12]

Further studies are needed to corroborate this initial single-institution experience. A well-designed multicenter clinical trial could demonstrate the wider applicability of this airway reconstructive strategy and could better define its role in lung cancer management. Other studies are needed to understand the mechanisms underlying tissue regeneration and the apparent homing of stem cells. Reconstruction of the

Review Article

Aortic allografts: final destination?—a summary of clinical tracheal substitutes

Sailay Siddiqi[1], Rayna de Wit[1], Stefan van der Heide[1], Egbert Oosterwijk[2], Ad Verhagen[1]

Considering Leonardo da Vinci's concept of "structure and function", the intriguing mechanistic question that rises at this point is: what is the impetus for these mesenchymal stem cells to differentiate to a cartilaginous lineage on a vascular matrix? One could assume that an aortic allograft carries properties for a vascular lineage and would attract rather endothelial progenitor cells or smooth muscle cells than mesenchymal stem cells and differentiation towards an airway environment. From a basic biological perspective, the concept of "structure and function" in this context remains out of the ordinary and stimulating. Further studies ought to focus on elucidating these questions on a deeper level in the future.

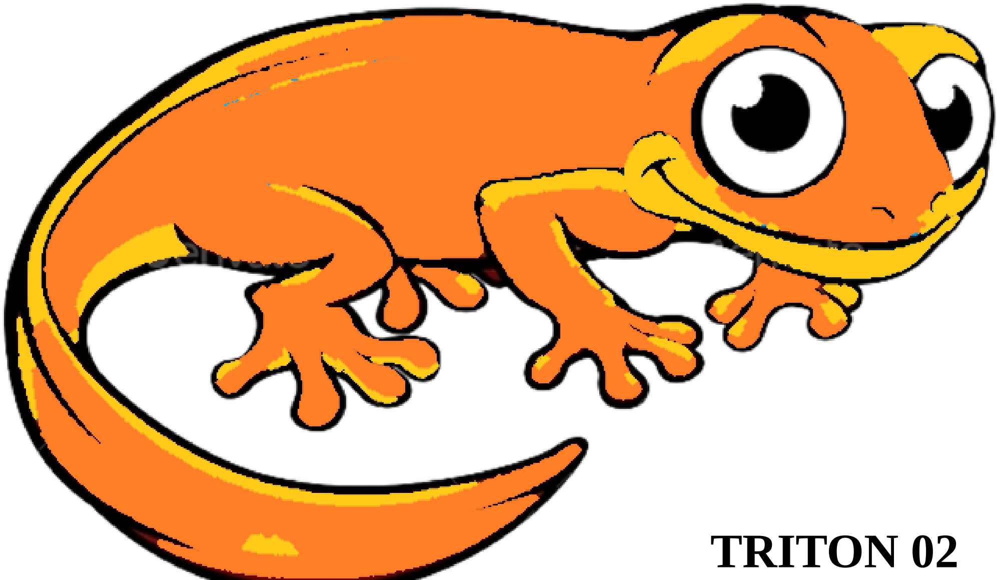
J Thorac Dis 2018;10(8):5149-5153

Tracheal Surgery : end-stage diseases
Lung Cancer Surgery : to avoid pneumonectomy
Regenerative Medicine

TRITON 02 Tracheal Replacement In ThyrOid caNcer (PHRC 2019)

Prospective multicentric randomized study, n=20 centers

Tracheal Replacement Using A Cryopreserved Aortic Allograft For R0 Resection In Locally Advanced Thyroid Cancer



TRITON 02

[Novel Reports]

CHEST

Successful Total Tracheal Replacement by Cryopreserved Aortic Allograft in a Patient Post-COVID-19 Infection

Cecilia Menna, MD; Claudio Andreetti, MD; Mohsen Ibrahim, MD; Anna Maria Ciccone, MD; Antonio D'Andrilli, MD; Giulio Maurizi, MD; Domenico M. Massullo, MD; Silvia Fiorelli, MD; and Erino A. Rendina, MD

This is the first report to our knowledge of a successful total tracheal replacement in a post-COVID-19 patient by cryopreserved aortic allograft. The graft was anastomosed to the cricoid and carina; a silicon stent was inserted to ensure patency. The patient was extubated on the operative table and was immediately able to breathe, speak, and swallow. No immunosuppression was administered. Three weeks after surgery, the patient was discharged from hospital in excellent health, and was able to resume his normal lifestyle, work, and activity as an amateur cyclist. Two months after surgery, the patient assumes aerosol with saline solution three times per day and no other therapy; routine bronchoscopy to clear secretions is no longer needed.

CHEST 2021; 160(6):e613-e617

KEY WORDS: COVID-19; cryopreserved aortic allograft; tracheal replacement

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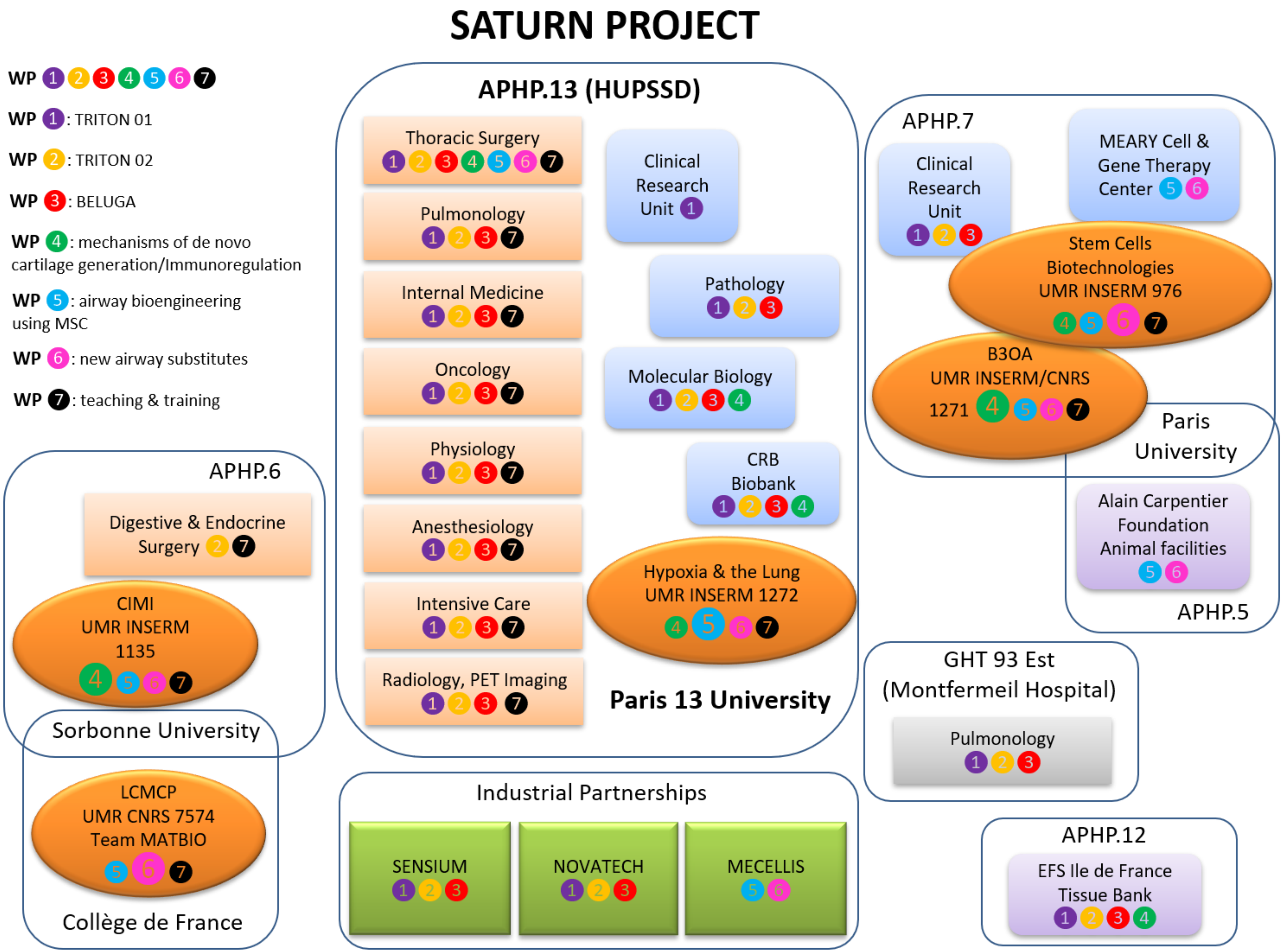
PROJECT


SATURN PROJECT
WP 1 2 3 4 5 6 7
WP 1: TRITON 01
WP 2: TRITON 02
WP 3: BELUGA
WP 4: mechanisms of de novo cartilage generation/Immunoregulation
WP 5: airway bioengineering using MSC
WP 6: new airway substitutes
WP 7: teaching & training
APHP.13 (HUPSSD)
Thoracic Surgery 1 2 3 4 5 6 7
Pulmonology 1 2 3 7
Internal Medicine 1 2 3 7
Oncology 1 2 3 7
Physiology 1 2 3 7
Anesthesiology 1 2 3 7
Intensive Care 1 2 3 7
Radiology, PET Imaging 1 2 3 7
Clinical Research Unit 1
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Molecular Biology 1 2 3 4
CRB Biobank 1 2 3 4
Hypoxia & the Lung UMR INSERM 1272 4 5 6 7
Paris 13 University
APHP.7
Clinical Research Unit 1 2 3
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Stem Cells Biotechnologies UMR INSERM 976 4 5 6 7
B3OA UMR INSERM/CNRS 1271 4 5 6 7
Paris University
Alain Carpentier Foundation Animal facilities 5 6
APHP.5
APHP.6
Digestive & Endocrine Surgery 2 7
CIMI UMR INSERM 1135 4 5 6 7
Sorbonne University
LCMCP UMR CNRS 7574 Team MATBIO 5 6 7
Collège de France
Industrial Partnerships
SENSIUM 1 2 3
NOVATECH 1 2 3
MECELLIS 5 6
GHT 93 Est (Montfermeil Hospital)
Pulmonology 1 2 3
APHP.12
EFS Ile de France Tissue Bank 1 2 3 4


thank you
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