Tracheal replacement

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ABSTRACT Tracheal reconstruction is one of the greatest challenges in thoracic surgery when direct end-to-end anastomosis is impossible or after this procedure has failed. The main indications for tracheal reconstruction include malignant tumours (squamous cell carcinoma, adenoid cystic carcinoma), tracheoesophageal fistula, trauma, unsuccessful surgical results for benign diseases and congenital stenosis. Tracheal substitutes can be classified into five types: 1) synthetic prosthesis; 2) allografts; 3) tracheal transplantation; 4) tissue engineering; and 5) autologous tissue composite. The ideal tracheal substitute is still unclear, but some techniques have shown promising clinical results. This article reviews the advantages and limitations of each technique used over the past few decades in clinical practice. The main limitation seems to be the capacity for tracheal tissue regeneration. The physiopathology behind this has yet to be fully understood. Research on stem cells sparked much interest and was thought to be a revolutionary technique; however, the poor long-term results of this approach highlight that there is a long way to go in this research field. Currently, an autologous tissue composite, with or without a tracheal allograft, is the only long-term working solution for every aetiology, despite its technical complexity and setbacks.

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Introduction

Tracheal reconstruction and replacement is a complex and vital surgical procedure with several indications, including primary tracheal neoplasm (adenoid cystic carcinoma and squamous cell carcinoma), thyroid cancer, extensive tracheoesophageal fistulas, unsuccessful previous surgery for benign tracheal diseases (re-stenosis, long-term stenosis that has been dilated or been non-surgically repaired) and, rarely, congenital tracheal stenosis. Primary tracheal resection with direct end-to-end anastomosis after release of the surrounding anatomical structures is insufficient when the length of trachea resected is greater than 50% in adults or 30% in children. Tracheal replacement with a substitute is then necessary to achieve healthy airway repair. The basics and principles of tracheal replacement were first described by Belsey [1] in 1950 and reviewed by Grillo [2] in 2002. The characteristics of an ideal tracheal replacement are summarised in table 1.

Furthermore, the substitute should not involve the use of growth factors, which are contraindicated in patients with cancer. Finally, in children, the tracheal replacement should increase in size with age in order to adapt to the patient's anatomy [3]. In contrast to the view of Belsey [1], an uninterrupted lining of ciliated columnar epithelium is not deemed necessary as long as the patient has an effective cough as a defence mechanism.

Numerous techniques have been used over the years in clinical practice to try to create the ideal tracheal replacement. The objective of this review is to describe each of these while highlighting their advantages and limitations.

Synthetic materials

Synthetic materials are, by definition, non-biocompatible and increase the risk of granulation, infection and erosion of adjacent organs [4]. The latter may lead to fistulas with surrounding vessels such as the aorta or the brachiocephalic artery, which increases the risk of life-threatening haemoptysis [5, 6]. Synthetic materials constitute an interface in the respiratory tract and provoke inflammatory granulomas that obstruct the lumen. They can also become colonised with microorganisms, causing purulent debris and halitosis [7]. Two main types of prosthesis have been described: solid and porous.

Solid prosthesis

Clinical trials with solid prostheses have mainly used the Neville prosthesis, a silicone rubber prosthesis with a non-terminal Dacron ring [8]. The prosthesis is telescopic, enabling easy integration into the tracheal lumen to facilitate placement. Between 1970 and 1988, Neville *et al.* [9] treated 35 patients with tracheal replacement, using either a straight prosthesis (n=27) (figure 1a) or a bifurcated prosthesis (n=8) (figure 1b). Of these 35 patients, 20 had a benign stenosis and the remaining 15 had a malignant tumour. Morbidity was high, with suture-line granulomas developing in 10 of these patients (29%). One patient had graft dehiscence that was replaced by a T-tube. Long-term evaluation of outcome was difficult because many patients were lost to follow-up.

Less favourable results were reported by Toomes *et al.* [5], who used a solid prosthesis in nine patients: three patients died, 10 days, 15 days and 4 weeks after surgery, from early complications. Two patients died later from complications related to the prosthesis after being discharged from the hospital: a fistula with the innominate artery and disunion of the distal anastomosis complicated by empyema and mediastinitis. One patient died 2 months after surgery and two others 4 months after surgery from their underlying disease. Only one patient was alive after 13 months of follow-up.

With such high morbidity and mortality, solid prostheses are not a long-term viable option for extensive tracheal replacement.

TABLE 1 Substitute characteristics for tracheal replacement

Substitute characteristics
Lateral rigidity and stiffness
Longitudinal flexibility
Airtight lumen
No need for immunosuppression
Reliable, feasible and reproducible technique
Biocompatible: integration to adjacent tissues and healing, so that chronic inflammation, granulation tissue, infection and erosion do not occur

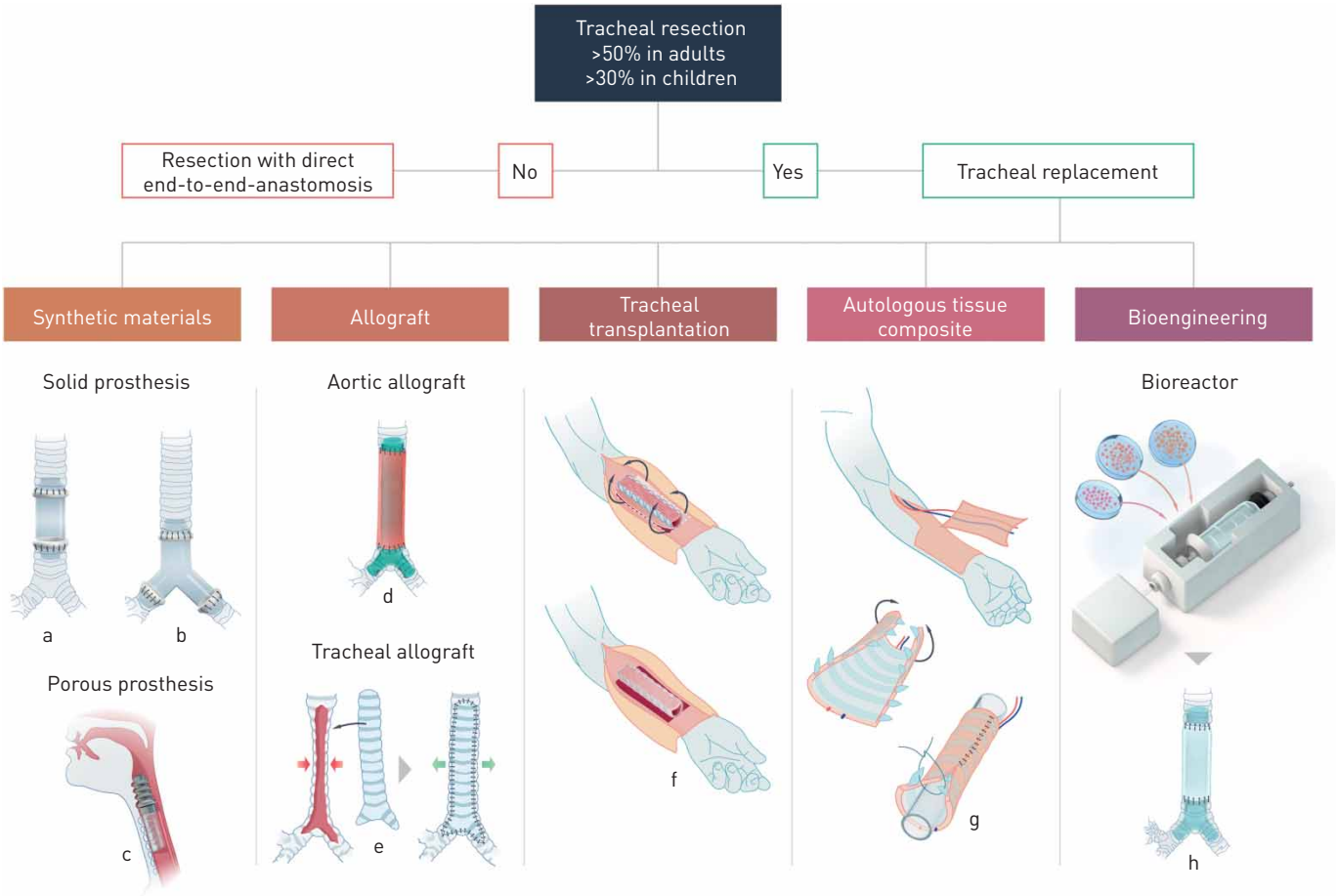

FIGURE 1 Different therapeutic options for tracheal replacement. a) Straight solid prosthesis [9]. b) Bifurcated solid prosthesis [9]. c) Porous titanium prosthesis used by Debry *et al.* [15] after laryngectomy. This approach is limited to the proximal part of the trachea associated with the larynx. d) Aortic allograft with a stent to maintain lateral rigidity [18]. e) Long tracheal stenosis treated by a tracheal allograft [21]. f) Positioning of the tracheal graft on the forearm to promote vascularisation and viability before transplantation in the orthotopic position [28]. g) Free fascio-cutaneous flap from the forearm reinforced by cartilage struts [36]. h) Stem cells seeding in the bioreactor before implantation of the bioengineered trachea [41].

Porous prosthesis

Compared with solid prostheses, porous prostheses should be more biocompatible, as their porous nature should allow ingrowth of connective tissue, initiating migration of the tracheal epithelium and further incorporating the prosthesis into the remaining tracheal tissue.

In a study by Maziak *et al.* [10], on 38 patients with adenoid cystic carcinoma of the airways, five patients underwent tracheal reconstruction with a Marlex mesh prosthesis. Four of these patients underwent surgery before 1968, when release manoeuvres of the trachea were unknown. When reviewed retrospectively, three of these patients could have been given a direct end-to-end anastomosis instead of a tracheal replacement with a synthetic substitute. One patient treated with prosthetic reconstruction died 2 weeks after surgery from a fistula between the trachea and innominate artery, caused by erosion of the artery by the Marlex mesh prosthesis. A second death followed resection of the trachea and carina with reconstruction using a Marlex mesh prosthesis. This patient died on postoperative day 10 after dehiscence of the lower end of the prosthesis, followed by bronchopneumonia and cardiac arrest. The other three patients had good long-term results of 2, 5 and 8 years. One of these patients had the Marlex mesh removed 5 years after the initial surgery because of severe narrowing of the upper anastomosis. A direct tracheal end-to-end anastomosis was performed after release procedures were used on the upper and lower airway.

Despite the high morbidity and mortality, research on tracheal replacement with a porous prosthesis has not been abandoned. Schultz and co-workers developed a tracheal prosthesis made of porous titanium with a double ring of bulk titanium [11]. The main objective was to use this prosthesis more like a laryngeal prosthesis in patients who have undergone total laryngectomy. After promising results in rats

(epithelisation inside the prosthesis, colonisation and integration of the prosthesis in surrounding tissues) [12], tests on larger animals were initially poor [13]. This was probably due to the absence of three key elements [11]: 1) systematic placement of a silicone tube inside the prosthesis to maintain the prosthesis calibre; 2) pre-conditioning of the prosthesis by attaching it to a muscle before replacing the trachea, which results in the development of connective tissue between the beads of the titanium prosthesis and its integration into the surrounding tissue; and 3) grafting mucosal epithelium from the buccal floor inside the prosthesis to accelerate ciliary respiratory epithelial regeneration.

Clinical use of this device has given promising results. A 56-year-old man who underwent total laryngectomy received this prosthesis (figure 1c). At 16-month follow-up, he could breathe and expectorate through the upper airway while closing his tracheostomy for several hours. There was no sign of infection or stenosis of the prosthesis, and the patient could eat normally with few swallowing problems [14, 15]. However, this approach is currently limited to the proximal part of the trachea associated with the larynx, and cannot be considered as a valuable technique for extended tracheal replacement.

Allografts

Allografts are biocompatible with the surrounding tissue when they are decellularised. Moreover, there is no need for immunosuppression nor growth factors, which makes this technique a potential candidate for oncological diseases. However, lack of specific vascularisation is responsible for degeneration of both tracheal and aortic allografts. In addition, lack of lateral rigidity, especially in aortic allografts, has to be compensated for by implementing a stent, which exposes the patient to chronic inflammation, granulation tissue, infection and erosion of adjacent structures. Finally, a tracheal allograft does not allow circumferential replacement of the trachea, which limits its indications, especially for oncological diseases.

Aortic allografts

In 2006, Azorin *et al.* [16] reported the first clinical replacement of a trachea with a fresh autologous abdominal aorta (figure 1d). The patient was a 68-year-old man with a squamous cell carcinoma of the trachea. A silicone Dumon stent was introduced into the aorta after replacing the trachea. The patient died 6 months after surgery from bilateral pneumonia and septic shock. The family refused permission for an autopsy.

The same team later reported the case of a 78-year-old man who, after superior bilobectomy, had his right main bronchus reconstructed with a cryopreserved aortic allograft, which was supported by a metallic stent in order to avoid pneumonectomy [17]. No evidence of mature cartilage regeneration was found during follow-up. The other concern was the lowered forced expiratory volume in 1 s (FEV_1) of 1.27 L, not too different from the predicted FEV_1 if the patient had undergone a pneumonectomy (preoperative FEV_1 2.8 L).

The largest study using cryopreserved aortic allograft was reported by Wurtz *et al.* [18]. Five men and one woman with large mucoepidermoid or adenoid cystic carcinomas of the trachea were included. Replacement was performed with a fresh, cryopreserved, descending thoracic aorta from cadaveric donors. To promote revascularisation of the graft and prevent erosion of contiguous large vessels, the allograft was wrapped in a pectoralis major muscle flap, pedicled to its thoraco-acromial blood supply. Four patients were alive and disease-free at the time the study was published, with a mean follow-up of 34 months (range 26–42 months). No patient received an allograft that was stiff enough to allow definitive stent withdrawal. Morbidity was high: tracheoesophageal fistula in two patients, anterior spinal cord ischaemia in one patient, multiple stent migration in one patient and a fatal massive haemoptysis from a fistula with a contiguous artery in one patient. Biopsies of the allografts showed no cartilage regeneration, and also showed inflammatory infiltrates in the allograft and the absence of a respiratory epithelium. These results were different to those reported in animal experiments. In a sheep model, Seguin *et al.* [19] showed that aortic autografts and fresh or cryopreserved allografts could be valuable tracheal or bronchial substitutes with *in situ* regeneration of cartilage and epithelium from the native airways, most probably from recipient stem cells. Cartilage regeneration was inconsistent in experimental studies, though: Tsukada *et al.* [20] found no confirmation of cartilage regeneration.

Another concern with aortic allografts is significant shortening of the graft, as reported by Wurtz *et al.* [18]. Tsukada *et al.* [20], using image analysis, found profound shortening of up to 87.5% of the grafted area at 1 year after implantation, secondary to axial shift of the native trachea and replacement by inflammatory tissue. Fresh aortic allografts do not promote tracheal regeneration after interposition and are associated with high morbidity owing to the presence of a permanent stent.

Tracheal allograft

In a report by Jacobs *et al.* [21], 24 children were treated with a tracheal allograft for congenital, post-traumatic and prolonged intubation stenosis (figure 1e). Cadaver tracheas were removed from donors aged 16–60 years old, within 24 h of death, either during multiorgan retrieval or at autopsy. The tracheas were placed in a tissue bank. After being chemically treated, all cells in the graft were dead and all major histocompatibility complex markers were lost. During the surgical procedure, an anterior incision was made in the portion of the trachea that had the stenosis and was continued in both cephalad and caudad direction until the normal trachea or bronchus were reached. The lateral walls of the narrowed segment were then removed, leaving only the posterior wall in continuity. A silicone stent was initially left in place to support the graft for 10–12 weeks until the graft healed and was colonised by a new epithelium. Follow-up ranged from 5 months to 10 years (3.79±0.7 years). Of the 24 patients, 20 (83%) survived and 16 of these had no airway problems. These patients had a stable and functional tracheal allografts with re-epithelisation of the lumen. The extremities of the allograft were colonised by the patient's native ciliary respiratory epithelium. This phenomenon was not observed in the mid-portion of the allograft. No patient had rejection or required immunosuppression. The cartilage showed no calcification. This technique is limited by the amount of tissue regeneration. Moreover, no evidence was found to suggest that the tracheal allograft would grow itself.

This initial report was followed by a North American experience in 1999 [22]. The technique used was the same as the one described previously [21]. Of six patients with congenital, post-traumatic and prolonged intubation stenosis, one died from a tracheal fistula with the innominate artery on day 12. Follow-up ranged from 0.57 to 2.44 years, with a mean follow-up of 1.68±0.39 years. Of the five survivors (83%), three, who had their stent removed, had tracheomalacia and required new stents. One of these patients had his stent removed completely and underwent frequent bronchoscopy for granulation removal, while another patient underwent stenting with a tracheostomy tube and was decannulated during follow-up. The final patient still had a tracheostomy and the stent in place at the most recent follow-up. Dramatic improvements in pulmonary function tests have been documented after tracheal allograft reconstruction.

More recently, Propst *et al.* [23] reported their experience with the same technique in 10 children: follow-up was marked by a high rate of re-interventions (average of 7.38 procedures per patient (range 1–19)). Re-interventions included minor procedures (granulation removal, tracheal dilation, endoscopic laser treatment, mitomycin application, stent placement, supraglottoplasty, endoscopic arytenoidectomy, tonsillectomy and adenoidectomy) as well as major procedures (laryngotracheoplasty and slide tracheoplasty). The operation-specific decannulation rate (patients who did not require any subsequent major open airway reconstruction before cannulation) for tracheal reconstruction using cadaveric allografts was 7% (1/14 tracheal reconstructions). The need for long-term tracheal cannulation involves malacia of the reconstruction and also indicates the poor mechanical results of such reconstruction.

Tracheal allografts enable extensive repair of tracheal stenosis. However, their place among current options remains unclear owing to the high morbidity rate. It seems more reasonable to use these allografts as a last resort after nonsurgical treatment, slide tracheoplasty, pericardial patch tracheoplasty and/or rib cartilage tracheoplasty have failed [21]. This technique is limited to benign lesions as the membranous posterior wall is left in place. Other limitations include: 1) the need for long-term tracheal stenting with its possible complications; 2) the development of serious malacia as the dead cartilage is resorbed and replaced by fibrosis; it is biologically inconceivable that completely dead cartilage could regenerate as living cartilage; and 3) the fact that the mid-portion of the tracheal allograft, especially when long segments are replaced, is not colonised by respiratory ciliary epithelium, unlike the extremities adjacent to the host's native tissue.

It appears that tracheal allografts cannot function as a template for regeneration of the complex tracheal structure: the high morbidity linked to their use, as demonstrated by the many re-interventions and the need for long-term cannulation, should encourage surgeons to find alternative techniques.

Tracheal transplantation

There are three main obstacles to the transplantation of tracheas.

1) The need for immunosuppressive therapy, which is not appropriate if dealing with a malignant tumour. Immunosuppression exposes the recipient to the risk of disease progression or faster relapse.

2) The complex blood supply to the trachea. This is ensured by a network of small blood vessels penetrating the trachea between the cartilage rings and originating from cervical arteries (inferior thyroid artery, left subclavian artery, left internal mammary artery, middle thyroid artery of Neubauer) and thoracic arteries (bronchial arteries). The arterial and venous supply to the trachea do not lend themselves easily to direct revascularisation as the vessels are of tiny diameter and have a segmental distribution. Attempts have been made mainly in animal models: Macedo *et al.* [24] showed in pigs that preservation of

the bronchial arteries as well as the inferior thyroid artery were needed to maintain viability of a long segment of circumferential tracheal replacement. Moreover, the surgeon is confronted with anatomical variations of tracheal vascularisation from one donor to the next.

3) The surgical technique: organ transplantation is very demanding and technically complex. In the case of tracheal transplantation, maintaining the entire blood supply to the trachea from two levels of arteries seems particularly challenging.

To overcome the need for direct revascularisation and simplify the surgical technique in order to make it easily reproducible, wrapping the tracheal transplant in heterotopic tissue from the recipient is an interesting alternative. This tissue is well vascularised and perfused by an identifiable vascular pedicle. This intervention can be performed as a one- or two-stage procedure.

In 1979, Rose *et al.* [25] reported the first allogenic tracheal transplantation in humans. The trachea was implanted heterotopically into the sternocleidomastoid muscle of the recipient and transferred into the orthotopic position after 3 weeks. In 1993, Levashov *et al.* [26] reported the case of a 24-year-old woman with idiopathic mediastinal fibrosis who had marked stenosis of the trachea because of this condition. She underwent one-stage tracheal transplantation with omentopexy of the graft. At postoperative day 10, the patient experienced signs of rejection, which were treated with corticosteroids and anti-thymocyte globulin. Four months after surgery, severe graft stenosis developed, which was treated with a silicone stent. Both reports, however, lack clear documentation of the viability of the allograft and the functional qualities of its different structures. No information was available regarding the long-term outcome. Klepetko *et al.* [27] also used the omentum to wrap a tracheal transplant but they opted for a two-stage procedure in a patient who was also undergoing bilateral lung transplantation for end-stage chronic pulmonary obstructive disease. Fortunately for the patient, after resection of the stenosis, the surgical team was able to reconstruct the trachea with a direct end-to-end anastomosis. 8 months after transplantation, pathological analysis of the graft, which was implanted in the omentum, showed a vital cartilage, covered with respiratory epithelium without signs of rejection. However, questions were left unanswered about what would have been the evolution of the graft if placed in the patient's lower airway tract.

The best clinical experience with this technique comes from Delaere *et al.* [28], who developed a two-stage technique in which the trachea from a donor was placed in the recipient's forearm (figure 1f). This allowed revascularisation of the graft, maintaining its viability before using it to correct the tracheal defect. The posterior tracheal wall was removed from the allograft and replaced with buccal mucosa from the recipient. Immunosuppressive therapy with tacrolimus, azathioprine and corticosteroids was started intravenously and maintained orally. The trachea was later transplanted into the recipient in the orthotopic position after verifying that the tissues were viable. The transplant was sutured into the airway defect and the radial vascular pedicle was sutured to the neck vessels.

The first patient to be treated was a 55-year-old woman who had undergone tracheotomy following a car accident 25 years earlier. She had a long history of tracheal stenosis and placement of stents to preserve the lumen, which were complicated by chronic infections (pneumonia, bronchitis), tissue granulation and halitosis. Chimerism between the donor and the recipient tissue occurred after the recipient buccal mucosa was introduced into the transplant. The endothelial and respiratory cells that originated from the donor disappeared shortly after the withdrawal of all immunosuppressive therapy.

Tracheal transplantation was performed in four additional patients [29]. In patient 2, after immunosuppressive therapy was stopped for 6 weeks, necrosis of most of the recipient and donor mucosal lining had occurred, and the cartilage rings had lost their support, making this transplant unsuitable for airway reconstruction. The reconstructed airway was not sufficient to maintain breathing in patient 4 and a tracheotomy was necessary. The reconstructed airway remained sufficient for normal breathing in patient 3. Allotransplantation was performed in patient 5 to treat an advanced low-grade chondrosarcoma of the larynx and trachea. Follow-up computed tomography scans showed a vascularised allograft associated with a well-healed anastomosis with the native airway. 6 months after orthotopic transplantation, the diameter of the reconstructed laryngeal and tracheal airways remained normal, without signs of tumour recurrence.

The limitations of this technique include the lack of circumferential revascularisation with necrosis of the posterior membranous wall, exposing the rest of the transplant to the same risk and the need for long-term immunosuppressive therapy, which makes it inappropriate for aggressive malignant tumours. Despite these drawbacks, the technique developed by Delaere and co-workers is a promising approach. Other reported cases and longer follow-up are needed to confirm the durability of this reconstruction technique.

Autologous tissue composite

We distinguished regional flaps (greater omentum flap [30], intercostal muscle flap [29], pectoralis major muscle flap [31] or sternocleidomastoid muscle flap) from free fascio-cutaneous flaps (radial forearm flap [32, 33] or anterolateral thigh flap [34]). The vascular autonomy of these tissues allows faster healing, greater reliability and better stability over time. Combining these grafts with a rigid structure reproduces the characteristics of the tracheal rings. Some surgical teams have opted for prosthetic materials to ensure rigidity: Maciejewski *et al.* [33] reported reconstruction of the trachea in a 34-year-old man with recurrent thyroid gland cancer infiltrating the trachea, using a left radial forearm flap as a tube and suspended to the biodegradable mesh rings placed outside by sutures. Similarly, Yu *et al.* [35] reconstructed a trachea after removal of an invasive thyroid tumour using a radial forearm free flap with a combined PolyMax mesh (Synthes, Paoli, PA, USA) and Hemashield vascular graft (Boston Scientific, Natick, MA, USA) for external rigid support. In both cases, no long-term data were available to evaluate the results of this technique.

The largest clinical experience was reported by Fabre *et al.* [36]. Instead of being reinforced with an external prosthesis, a free fascio-cutaneous flap from the forearm was reinforced with cartilage struts (figure 1g) [37]. In this technique, the cartilage provides transverse rigidity while the skin provides longitudinal elasticity and an epithelium for the lumen. As the graft involves autologous tissues, there is no risk for acute or chronic rejection. Unlike grafts made from synthetic materials, chronic inflammation or infection is not a problem. The main limitation of the newly reconstructed trachea is the lack of mucociliary clearance. Ciliary respiratory epithelium is not a prerequisite for tracheal replacement as long as the patient has an effective cough [2]. Therefore, the lack of spontaneous mucociliary clearance within the neo-trachea requires aggressive management of bronchial secretions postoperatively. Another limitation is the risk of cartilage fracture in case of extensive calcifications in elderly patients. This technique seems to be inappropriate for patients who lack excellent diaphragmatic and respiratory mechanical function to make them capable of effective coughing [38]. Between August 2004 and April 2015, 16 patients were treated at the Marie Lannelongue University Hospital: 12 for primary tracheal neoplasms (nine adenoid cystic carcinomas and three squamous cell carcinomas), three secondary tracheal neoplasms (one thyroid carcinoma and two tracheal lymphomas) and one post-intubation extended tracheal destruction after a long history of stenting [36]. The 5-year survival rate was 64.8%. One patient with chronic severe respiratory insufficiency required a distal short stent and two other patients required a permanent tracheostomy. The two patients who reported dysphagia before the procedure due to extensive tracheoesophageal fistulas were able to resume oral feeding after surgery. Repeated endoscopies and dynamic computed tomography scans demonstrated satisfactory patency of the neo-trachea without inspiratory collapse, both during the early postoperative period and several years after the procedure.

Tissue engineering

Tissue engineering allows *in vitro* or *in vivo* creation of tracheal tissues by associating a three-dimensional matrix with stem cells cultivated *in vitro* and originating from the patient. No immunosuppressive therapy is needed after surgery: theoretically, this is a promising pathway that would offer selected patients an ideal tracheal replacement. Furthermore, it could also open new fields for tissue regeneration in other organs.

In 2008, Macchiarini *et al.* [39] presented the first case of a 30-year-old woman with severe bronchomalacia, who had her left main bronchus replaced with a human donor trachea, which was colonised in a bioreactor by epithelial cells and mesenchymal stem-cell-derived chondrocytes originating from the patient. The authors stated that the graft immediately provided the recipient with a functional airway, improved her quality of life, and had a normal appearance and mechanical properties after 4 months. However, long-term follow-up was complicated. The patient's airway narrowed again and collapsed, requiring clinicians to insert a stent to keep her airway open. The stent was removed after 6 months but the patient had several more stents inserted and removed over the years [40]. Eventually, a left pneumonectomy was performed in 2016, owing to graft failure, chronic lung infection and colonisation, and uncountable number of bronchoscopic procedures. Other published cases followed from Elliott *et al.* [3] and Jungebluth *et al.* [41]. Jungebluth *et al.* [41] published the case of a 36-year-old man who presented with recurrent primary cancer of the distal trachea and main bronchi. The airway was replaced with a tailor-made bioartificial nanocomposite previously seeded with autologous bone-marrow mononuclear cells *via* a bioreactor for 36 h (figure 1h). The authors stated that there were no major complications, and the patient was asymptomatic and tumour-free 5 months after surgery. The bioartificial nanocomposite had patent anastomoses, was lined with a vascularised newly formed mucosa, and was partly covered by healthy epithelium. What would appear as a revolution in tracheal replacement, and more broadly in organ tissue regeneration, soon had the entire medical community's attention [42, 43] and also drew much media attention [44].

Studies on pigs by Birchall and Macchiarini, carried out before the first clinical case, were never published [40]. The mechanisms behind colonisation of the matrix by stem cells, ending up in the production of tracheal tissue with regeneration of a full-thickness epithelial lining, despite the initial mucosal defects, were not clear. Regeneration within the airway tract is only possible for epithelial defects above the basement membrane. If tissue injury is severe and involves damage to both the epithelial and the submucosal layers, tissue regeneration is not possible, and healing leads to fibrosis and subsequent stenosis of the new trachea. Investigations by independent parties resulted in concerns of scientific misconduct by Jungebluth and co-workers in their case report: contrary to what the authors stated, bronchoscopy reports revealed the need for stents to stabilise the airway [45]. Moreover, epithelisation of the graft was unproven as no biopsy reports of the healthy growth of epithelial structures could be found [46]. The patient developed serious complications leading to death [45].

The so-called bioengineered tracheal replacement appears to be more like a simple bioprosthesis or a synthetic prosthesis, depending on what material is used for the scaffold. The protocol for seeding stem cells on it did not lead to tissue regeneration. More experimental research in regenerative medicine is necessary to completely understand this field and the physiopathology behind it before any relevant clinical application is reached.

Conclusion

Extensive tracheal replacement remains one of the greatest challenges in thoracic surgery when direct end-to-end anastomosis is impossible or has failed. Different attempts to achieve it using diverse approaches have been made, including synthetic prosthesis, allografts, autologous tissue composite, tracheal transplantation and tissue engineering. None of them has been shown to be the ideal tracheal replacement. However, promising results have been obtained with some of them, as shown by tracheal transplantation and free forearm flap reinforced with cartilage struts. Compared with tracheal transplantation, indications for autologous replacement can be extended to malignant tumours as no immunosuppressive therapy is required. The absence of a mucociliary respiratory epithelium is the main limitation for autologous reconstruction, requiring aggressive management of postoperative secretions. Further research in tracheal replacement is necessary in order to optimise existing techniques, discover new ones and understand the complex physiopathology behind tissue regeneration and stem cell use.

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References

1 Belsey R. Resection and reconstruction of the intrathoracic trachea. *Br J Surg* 1950; 38: 200–205.
2 Grillo HC. Tracheal replacement: a critical review. *Ann Thorac Surg* 2002; 73: 1995–2004.
3 Elliott MJ, De Coppi P, Speggiorin S, *et al.* Stem-cell-based, tissue engineered tracheal replacement in a child: a 2-year follow-up study. *Lancet* 2012; 380: 994–1000.
4 Doss AE, Dunn SS, Kucera KA, *et al.* Tracheal replacements: Part 2. *ASAIO J* 2007; 53: 631–639.
5 Toomes H, Mickisch G, Vogt-Moykopf I. Experiences with prosthetic reconstruction of the trachea and bifurcation. *Thorax* 1985; 40: 32–37.
6 Deslauriers J, Ginsberg RJ, Nelems JM, *et al.* Innominate artery rupture. A major complication of tracheal surgery. *Ann Thorac Surg* 1975; 20: 671–677.
7 Gaissert HA, Grillo HC, Wright CD, *et al.* Complication of benign tracheobronchial strictures by self-expanding metal stents. *J Thorac Cardiovasc Surg* 2003; 126: 744–747.
8 Neville WE, Bolanowski PJ, Soltanzadeh H. Prosthetic reconstruction of the trachea and carina. *J Thorac Cardiovasc Surg* 1976; 72: 525–538.
9 Neville WE, Bolanowski JP, Kotia GG. Clinical experience with the silicone tracheal prosthesis. *J Thorac Cardiovasc Surg* 1990; 99: 604–612.
10 Maziak DE, Todd TR, Keshavjee SH, *et al.* Adenoid cystic carcinoma of the airway: thirty-two-year experience. *J Thorac Cardiovasc Surg* 1996; 112: 1522–1531.
11 Dupret-Bories A, Schultz P, Vrana NE, *et al.* Development of surgical protocol for implantation of tracheal prostheses in sheep. *J Rehabil Res Dev* 2011; 48: 851–864.
12 Schultz P, Vautier D, Chluba J, *et al.* Survival analysis of rats implanted with porous titanium tracheal prosthesis. *Ann Thorac Surg* 2002; 73: 1747–1751.
13 Schultz P, Vautier D, Charpiot A, *et al.* Development of tracheal prostheses made of porous titanium: a study on sheep. *Eur Arch Otorhinolaryngol* 2007; 264: 433–438.
14 Debry C, Dupret-Bories A, Vrana NE, *et al.* Laryngeal replacement with an artificial larynx after total laryngectomy: the possibility of restoring larynx functionality in the future. *Head Neck* 2014; 36: 1669–1673.
15 Debry C, Vrana NE, Dupret-Bories A. Implantation of an artificial larynx after total laryngectomy. *N Engl J Med* 2017: 97–98.
16 Azorin JF, Bertin F, Martinod E, *et al.* Tracheal replacement with an aortic autograft. *Eur J Cardiothorac Surg* 2006; 29: 261–263.
17 Martinod E, Radu DM, Chouahnia K, *et al.* Human transplantation of a biologic airway substitute in conservative lung cancer surgery. *Ann Thorac Surg* 2011; 91: 837–842.

18 Wurtz A, Porte H, Conti M, *et al.* Surgical technique and results of tracheal and carinal replacement with aortic allografts for salivary gland-type carcinoma. *J Thorac Cardiovasc Surg* 2010; 140: 387–393.
19 Seguin A, Radu D, Holder-Espinasse M, *et al.* Tracheal replacement with cryopreserved, decellularized, or glutaraldehyde-treated aortic allografts. *Ann Thorac Surg* 2009; 87: 861–867.
20 Tsukada H, Ernst A, Gangadharan S, *et al.* Tracheal replacement with a silicone-stented, fresh aortic allograft in sheep. *Ann Thorac Surg* 2010; 89: 253–258.
21 Jacobs JP, Elliott MJ, Haw MP, *et al.* Pediatric tracheal homograft reconstruction: a novel approach to complex tracheal stenoses in children. *J Thorac Cardiovasc Surg* 1996; 112: 1549–1558.
22 Jacobs JP, Quintessenza JA, Andrews T, *et al.* Tracheal allograft reconstruction: the total North American and worldwide pediatric experiences. *Ann Thorac Surg* 1999; 68: 1043–1051.
23 Propst EJ, Prager JD, Meinzen-Derr J, *et al.* Pediatric tracheal reconstruction using cadaveric homograft. *Arch Otolaryngol Head Neck Surg* 2011; 137: 583–590.
24 Macedo A, Fadel E, Mazmanian GM, *et al.* Heterotopic en bloc tracheobronchial transplantation with direct revascularization in pigs. *J Thorac Cardiovasc Surg* 2004; 127: 1593–1601.
25 Rose KG, Sesterhenn K, Wustrow F. Tracheal allotransplantation in man. *Lancet* 1979; 1: 433.
26 Levashov Yu N, Yablonsky PK, Cherny SM, *et al.* One-stage allotransplantation of thoracic segment of the trachea in a patient with idiopathic fibrosing mediastinitis and marked tracheal stenosis. *Eur J Cardiothorac Surg* 1993; 7: 383–386.
27 Klepetko W, Marta GM, Wisser W, *et al.* Heterotopic tracheal transplantation with omentum wrapping in the abdominal position preserves functional and structural integrity of a human tracheal allograft. *J Thorac Cardiovasc Surg* 2004; 127: 862–867.
28 Delaere P, Vranckx J, Verleden G, *et al.* Tracheal allotransplantation after withdrawal of immunosuppressive therapy. *N Engl J Med* 2010; 362: 138–145.
29 Delaere PR, Vranckx JJ, Meulemans J, *et al.* Learning curve in tracheal allotransplantation. *Am J Transplant* 2012; 12: 2538–2545.
30 Spaggiari L, Calabrese LS, D'Aiuto M, *et al.* Successful subtotal tracheal replacement (using a skin/omental graft) for dehiscence after a resection for thyroid cancer. *J Thorac Cardiovasc Surg* 2005; 129: 1455–1456.
31 Shinohara H, Yuzuriha S, Matsuo K, *et al.* Tracheal reconstruction with a prefabricated deltopectoral flap combined with costal cartilage graft and palatal mucosal graft. *Ann Plast Surg* 2004; 53: 278–281.
32 Beldholm BR, Wilson MK, Gallagher RM, *et al.* Reconstruction of the trachea with a tubed radial forearm free flap. *J Thorac Cardiovasc Surg* 2003; 126: 545–550.
33 Maciejewski A, Szymczyk C, Półtorak S, *et al.* Tracheal reconstruction with the use of radial forearm free flap combined with biodegradative mesh suspension. *Ann Thorac Surg* 2009; 87: 608–610.
34 Caliceti U, Piccin O, Cavicchi O, *et al.* Anterolateral thigh free flap for tracheal reconstruction after parastomal recurrence. *Head Neck* 2009; 31: 1107–1111.
35 Yu P, Clayman GL, Walsh GL. Human tracheal reconstruction with a composite radial forearm free flap and prosthesis. *Ann Thorac Surg* 2006; 81: 714–716.
36 Fabre D, Fadel E, Mussot S, *et al.* Autologous tracheal replacement for cancer. *Chin Clin Oncol China* 2015; 4: 46.
37 Fabre D, Singhal S, De Montpreville V, *et al.* Composite cervical skin and cartilage flap provides a novel large airway substitute after long-segment tracheal resection. *J Thorac Cardiovasc Surg* 2009; 138: 32–39.
38 Fabre D, Kolb F, Fadel E, *et al.* Successful tracheal replacement in humans using autologous tissues: an 8-year experience. *Ann Thorac Surg* 2013; 96: 1146–1155.
39 Macchiarini P, Jungebluth P, Go T, *et al.* Clinical transplantation of a tissue-engineered airway. *Lancet* 2008; 372: 2023–2030.
40 Vogel G. Trachea transplants test the limits. *Science* 2013; 340: 266–268.
41 Jungebluth P, Alici E, Baiguera S, *et al.* Tracheobronchial transplantation with a stem-cell-seeded bioartificial nanocomposite: a proof-of-concept study. *Lancet* 2011; 378: 1997–2004.
42 Delaere PR, Van Raemdonck D. The trachea: the first tissue-engineered organ? *J Thorac Cardiovasc Surg* 2014; 147: 1128–1132.
43 Delaere P, Van Raemdonck D. Tracheal replacement. *J Thorac Dis* 2016; 8: Suppl. 2, S186–S196.
44 Fountain H. A first: organs tailor-made with body's own cells. http://www.nytimes.com/2012/09/16/health/research/scientists-make-progress-in-tailor-made-organs.html The New York Times, September 15, 2012.
45 Claesson-Welsh L, Hansson GK, Royal Swedish Academy of Sciences. Tracheobronchial transplantation: The Royal Swedish Academy of Sciences' concerns. *Lancet* 2016; 387: 942.
46 Cyranoski D. Investigations launched into artificial tracheas. *Nature* 2014; 516: 16–17.