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REVIEW ARTICLE
Reconstructive

Advances in Tracheal Reconstruction

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Summary: A recent revival of global interest for reconstruction of long-segment tracheal defects, which represents one of the most interesting and complex problems in head and neck and thoracic reconstructive surgery, has been witnessed. The trachea functions as a conduit for air, and its subunits including the epithelial layer, hyaline cartilage, and segmental blood supply make it particularly challenging to reconstruct. A myriad of attempts at replacing the trachea have been described. These along with the anatomy, indications, and approaches including microsurgical tracheal reconstruction will be reviewed. Novel techniques such as tissue-engineering approaches will also be discussed. Multiple attempts at replacing the trachea with synthetic scaffolds have been met with failure. The main lesson learned from such failures is that the trachea must not be treated as a "simple tube." Understanding the anatomy, developmental biology, physiology, and diseases affecting the trachea are required for solving this problem. *(Plast Reconstr Surg Glob Open 2014;2:e178; doi: 10.1097/GOX.0000000000000097; Published online 9 July 2014.)*

ANATOMY AND BLOOD SUPPLY

The trachea connects the larynx to the carina, extending from the cricoid cartilage to its bifurcation into the left and right main bronchi. Anteriorly, it is composed of horseshoe-shaped cartilagenous rings making up two thirds of its circumference and posteriorly by a membranous portion connecting the rings.[1] In the neck, it is covered by the cervical fascia and infrahyoid muscles, crossed by the isthmus of the thyroid and the jugular venous arch. The carotid sheath and inferior thyroid artery are lateral to the trachea, the esophagus—posterior, and the recurrent laryngeal nerve lies in the groove between the two. In the thorax, it is crossed by the brachiocephalic artery and the left brachiocephalic vein.[2]

The trachea functions as a conduit for ventilation, clears secretions, warms, humidifies and cleans the air for the respiratory zone, and keeps the airway free of foreign material through coughing and intrinsic defense mechanisms.[3,4] The microanatomy of the trachea consists of a pseudostratified ciliated epithelium composed of ciliated cells, goblet cells, basal cells, and neuroendocrine cells[4,5] (Fig. 1). The submucosa is rich in elastin, submucosal glands, and smooth muscle. The cartilage is of a hyaline nature.[4] The tracheal walls are composed of 15–20 incomplete cartilaginous rings joined together by fibrous tissue and smooth muscle.[2] The tracheal lumen is generally ovoid in shape although variations appear even without disease. This lumen flattens anteroposteriorly. Two thirds of the circumference of the trachea is composed of normally C-shaped (or horseshoe-shaped) rings anteriorly while the rest is composed of a flat posterior membranous wall. This posterior wall is made of a thin membrane supported by the trachealis muscle.[3] There are about 2 rings per centimeter of trachea (see Figure 2 for photograph of a human trachea).

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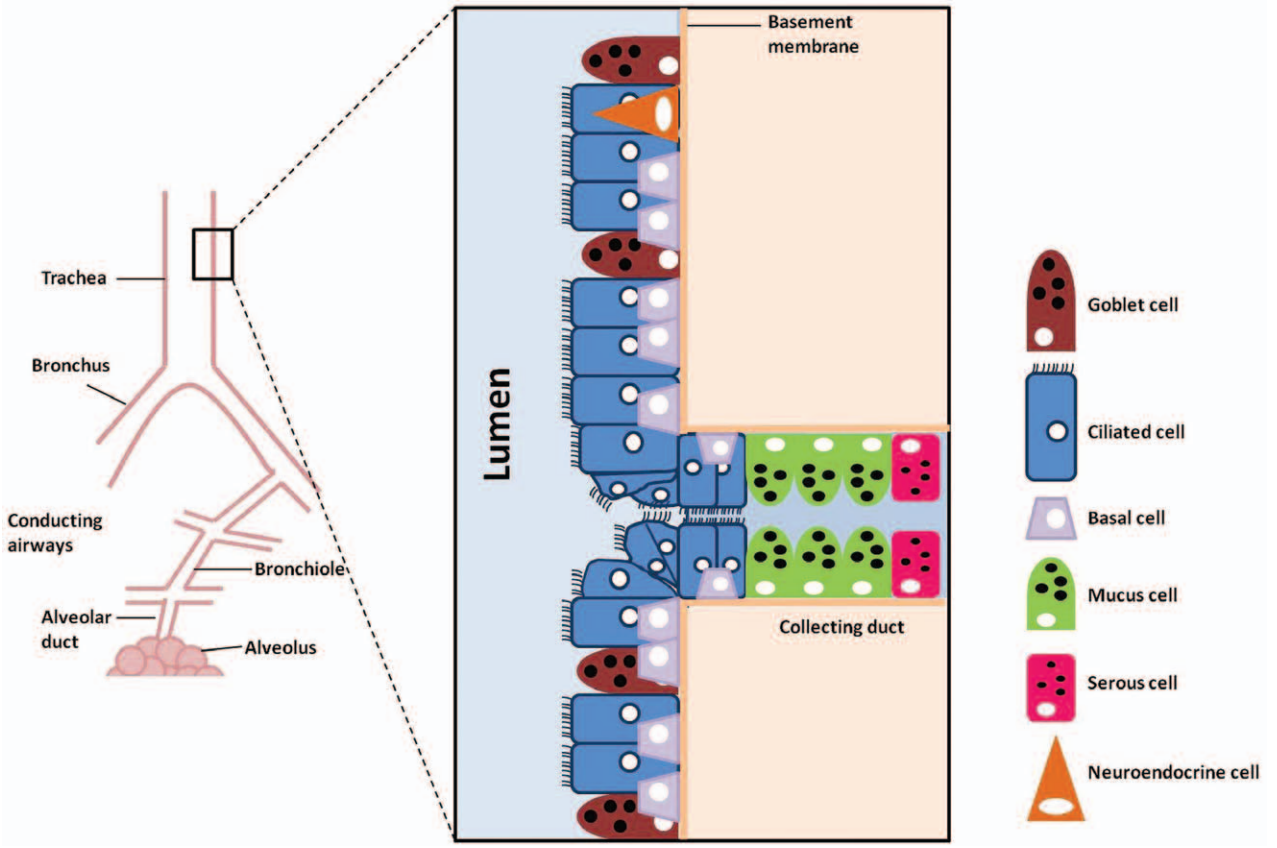

Fig. 1. Cellular composition of the human tracheal epithelium.

The trachea's blood supply comes from its lateral pedicles, vessels which originate from the inferior thyroid, subclavian, supreme intercostal, internal thoracic, innominate, and superior and middle bronchial arteries.[6] All of these vessels interconnect along the lateral surface and form important longitudinal vascular anastomoses. The lateral and anterior tracheal walls receive their blood supply from transverse segmental vessels which extend from these 2 lateral longitudinal networks and run between the cartilage rings. The transverse vessels feed capillary beds beneath the endotracheal mucosa that nourish the cartilage by diffusion. The esophageal arteries and their subdivisions supply the posterior membranous portion only.[6] The trachea's intricate blood supply makes devascularization easy and reconstruction especially challenging.

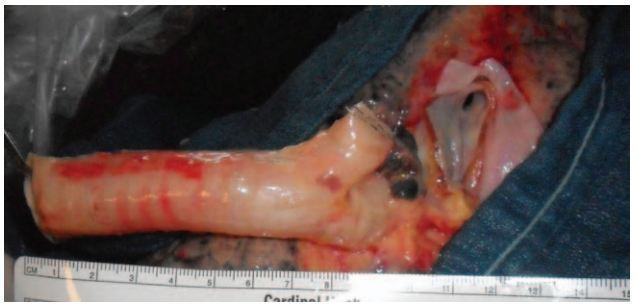

Fig. 2. Human trachea harvested intraoperatively from donor lung used for transplantation.

TRACHEAL REPLACEMENTS

Indications

The indications for tracheal replacement are lesions that cannot be resected and reconstructed safely with end-to-end anastomosis or long-segment congenital stenosis, which cannot be effectively managed with slide or patch tracheoplasty. Acquired lesions include malignancy, traumatic injury, and subglottic or tracheal stenosis. The general limits for safe resection are about one half of the tracheal length in adults and one third in small children. Very lengthy lesions that cannot be safely removed and reconstructed primarily are managed palliatively with long-term T-tubes or stents. The clinical course of these patients is usually complicated with multiple infections and frequent hospital admissions. Therefore, a safe and dependable tracheal replacement remains an important unmet need.

Requirements

The requirements for tracheal replacements are to be laterally rigid but longitudinally flexible, to have a surface composed of ciliated respiratory epithelium (although some authors have considered this not essential), or at least to have a surface which facilitates epithelial resurfacing. They must also be biocompatible, nontoxic, nonimmunogenic, and noncarcinogenic. They must not dislocate or erode over time, avoid accumulation of secretions, resist bacterial colonization, and must be permanent.

Approaches

The approaches used for tracheal replacement include stents and synthetic prostheses and scaffolds and are summarized in Table 1. The use of autologous tissues in combination with synthetic material is summarized in Table 2. The most interesting recent advances in the field of tracheal reconstruction pertain to tracheal transplantation and tissue engineering and are described in further detail.

TRACHEAL TRANSPLANTATION

Nonrevascularized Grafts

Autografts

Tracheal excision and immediate orthotopic reimplantation (fresh autograft) often fail due to a delay in revascularization.[46,72–75] However, this depends on the length of the autograft.[74,76] Despite possible survival in short segments, the cartilage eventually resorbed and the segment was replaced with fibrous tissue.[77] In longer segments, dissolution, stenosis, and obstruction followed due to loss of blood supply.[74] A new experimental technique using composite cervical skin and a costal cartilage flap has shown some promise over long segments although long-term follow-up is required.[78]

Allografts

Fresh tracheal allografts without immunosuppression will lead to rejection.[35,76,79,80] Rejection of fresh allografts of any length occurs even with immunosuppression, in the absence of revascularization.[26,63,74,77] All these grafts necrose, liquefy, or result in stenosis. Preserved and devascularized allografts also failed due to cartilage resorption, scar replacement, fibrosis, and eventual complete obstruction.[46,76,81,82] Cryopreserved allografts for small window defects[83] and short segments[84] reepithelialized but failed over longer lengths.[85] Patients transplanted with chemically fixed allografts for noncircumferential defects required multiple subsequent operations with a decannulation rate of only 60% in children and even lower in the adult population.[86] The literature implies that blood supply is critical for successful transplantation.

Table 1. Tracheal Replacements: Stents, Synthetic Prostheses and scaffolds, and Nonviable Tissue

Stents		
Silicone[7,8]	Advantages Removable Inert Adjustable Minimal granulation tissue	Disadvantages Difficult placement Tend to dislodge Lack of reepithelialization led to obstruction
Metallic[8,9]	Advantages Ease of placement with local anesthesia Higher internal: external diameter Less obstruction	Disadvantages Permanent Difficult to adjust and remove
Bioabsorbable[10–12]	Advantages Promote epithelialization Provide rigidity	Disadvantages Long-term modeling remains to be determined
Synthetic prostheses and scaffolds		
Solid	Materials Stainless steel[13] Steel coil[14] Silicone[15,16] Polythene[17,18] Teflon[19] Hydroxylapatite[20,21]	Disadvantages[22] Many patients suffered from obstructive granulation tissue and vascular erosion Required longer resections of previously native trachea Prompted development of porous structures
Porous	Materials[22, 23] Meshes supported to prevent air leakage with: Foreign material[24–34] Sealed with tissues[35–39] Biopolymers[32,40–42]	Disadvantages[22] Overgrowth with scar tissue Eventual obstruction and stenosis
Nonviable tissue		
Cadaveric tissue Fixed, frozen, lyophilized tissues	Advantages Rejection avoided[43,44]	Disadvantages Replaced with granulation and scar tissue[45] Necrosis of cartilage and epithelium[46–48]

Table 2. Tracheal Replacements: Autologous Tissues ± Synthetic Material

	Materials	Outcomes
Autologous tissues ± synthetic material		
Free grafts	Materials	Perichondrium on fascial flaps formed cartilage, reepithelialized but eventually stenosed
	Fascia[26,49,50]	Nasal cartilage resorbed
	Diced cartilage[14]	Bladder mucosa led to edema and obstruction
	Dermal grafts[51]	Patch graft with costal cartilage and pericardium successfully treated long congenital stenosis
	Pericardium[39]	Cartilage resorbed
	Omentum[38]	Pericardium replaced with mature scar tissue
	Periosteum[52,53]	Tracheal growth reduced
	Perichondrium[54]	A similar patch graft used in adult maintained patent airway over 2-year period
	Buccal mucosa + auricular cartilage[55]	
	Dura mater[56]	
	Bladder mucosa[57]	
	Periosteum[52,53]	
	Jejunal patches[58]	
Vascularized flaps	Materials	All met with limited success with few reports of long-term follow-up
	Pedicled intercostal latissimus dorsi[59]	
	Trapezius muscle[60]	
	Periosteum[61]	
	Buccal mucosa[61]	
	Proplast + skin flaps + conchal cartilage[62]	
Tube reconstruction	Materials	All required long multistage operations resulting in many complications (infections and failure to heal)
	Tubed pedicles (skin grafts + rib and costal cartilage)[63]	
	Polypropylene rings between dermis and platysma[64]	
	Cartilage hemirings from costal arches[65]	
	Aorta[66–68]	
	Esophagus[69–71]	

Vascularized Grafts

Autografts

Revascularization of fresh short-segment tracheal autografts was performed using omentum,[87–89] intercostal muscle,[90] deltopectoral muscle,[91] pectoralis major muscle,[92] free costal cartilage grafts,[93] chondromuscular flaps,[94] musculofascial flaps,[95] or other vascular pedicles such as the latissimus dorsi.[59,60] Omental flaps longer than 4 cm frequently resulted in ischemic tracheal segments and stenosis.[96] Preliminary implantation into a vascularized tissue or flap with delayed transfer into the defect has proven to be more successful.[38]

Allografts

Nontracheal allografts, such as fresh and cryoperserved allogeneic aorta, required no immunosuppression and had no graft rejection in most cases. However, aortic grafts were deemed unsuitable for tracheal replacement because of failure to regenerate and incorporate recipient tissue, requiring stenting and/or retransplantation.[97,98]

In tracheal allografts, the epithelium is the major site of antigenicity and removal with a detergent[99] or irradiation[100] was thought to prevent rejection.[101–104] Reepithelialization occurred by migration from the host epithelium[105] while the chondrocytes remained of donor origin.[106] However, complete epithelial regeneration failed and allografts were eventually rejected.[107] Other studies focused on providing immunosuppression, which allows for initial revascularization of a heterotopically transplanted graft to improve success of orthotopic allotransplantation.[108,109]

The first clinical tracheal allotransplantation was reported in 1979, where a donor trachea was first implanted heterotopically under the sternocleidomastoid muscle and pedicled orthotopically after 3 weeks.[110] No immunosuppression was required, and short-term integration with surrounding tissue and reepithelialization was achieved. Another case, later performed with omental revascularization and immunosuppression, eventually led to necrosis and stenosis requiring stent placement.[111]

Direct Revascularization

The blood supply to the trachea makes it challenging for direct revascularization. A composite graft composed of a thyrotracheal graft with anastomoses of the thyroid artery to the common carotid artery[112] has been attempted. Venous anastomosis was also required to prevent soft-tissue necrosis.[113,114] Long-term results have not been reported.

There is also an expanding role for free flaps to allow for revascularization of autografts and allografts. Their long-term outcomes for large tracheal defects have been reviewed by Yu et al.[115] The free flaps used include radial forearm flap,[115–118] anterolateral thigh

flap,[119,120] sternohyoid muscle,[121] and a saphenous corticoperiostal flap.[122]

Clinically, the transplantation of a fresh laryngeal allograft was performed to replace a stenotic larynx following a motorcycle accident. This allograft also included a 5-ring segment of trachea, thyroid, parathyroids, a portion of the attached pharyngeal wall, both superior laryngeal nerves, and the right recurrent nerve. Arterial, venous, and neural anastomoses were performed, and perfusion was established early in the procedure. Over time, the patient regained vocal cord function and normal deglutition. Despite one episode of rejection, health and function were good at 40 months, with continued immunosuppression.[123]

In 2010, a donor tracheal allograft was initially heterotopically transplanted under the forearm fascia to allow for indirect revascularization in an immunosuppressed patient. The donor posterior membranous part necrosed and was replaced with the recipient's buccal mucosa. The graft was subsequently moved to the orthotopic position, by which time the patient no longer required immunosuppression. The graft was fully lined with both donor and recipient epithelium and had viable donor tracheal cartilage surrounded by recipient blood vessels. It was harvested on a radial forearm free flap and inserted into a 4.5-cm defect.[124] Recently, they have moved toward the use of autologous cells as reepithelialization was found to be very slow with the use of a buccal mucosa (unpublished results).

TRACHEAL TISSUE ENGINEERING

The long-term risks of chronic immunosuppression and their contraindications in malignant disease have led to interest in tissue-engineering techniques.

The use of the term "tissue engineering" implies the replacement of tissues and organs by isolation and culture of cells outside the body, which are seeded later into a biocompatible scaffold before implantation. The 3 components required for tissue engineering are cells, scaffolds, and bioreactors.

Cells

Epithelial Cells

In the trachea, resident epithelial cells are located along the basal layer. These cells can be isolated, cultured, and differentiated in vitro.[125–128] Nontracheal exogenous cells that can be used for epithelial regeneration include embryonic stem cells, induced pluripotent stem cells, and cells from mesenchymal origin such as mesenchymal stem cells, human amniotic fluid stem cells, and umbilical blood cord–derived stem cells.[129]

Chondrocytes

Regeneration of endogenous cartilage can be stimulated in vivo by implantation of a gelatin sponge slowly releasing basic fibroblast growth factor[130,131] or bone morphogenetic protein 2.[132,133] The regenerated cartilage is of fibrous rather than hyaline nature. Autologous sources of chondrocytes include the nose, ribs, and ear, and these have been isolated and expanded in vitro in cell flasks and in a 3-dimensional culture system.[134–138] Despite the formation of a well-vascularized neotrachea, these scaffold-free constructs showed signs of mechanical failure. Allogeneic chondrocytes have also been used for the repair of joint cartilage and are intriguing due to their low antigenicity.[139,140]

The exogenous use of autologous stem/progenitor cells has been considered as a safer alternative and a better option for cell amplification. These include autologous adipose-derived stem cells and mesenchymal stromal cells and induced pluripotent stem cells.[141]

Scaffolds

Synthetic

The advantages of synthetic scaffolds include tailoring of size and shape and the ability to control their properties such as strength, degradation time, porosity, and microstructure. However, they lack the macro- and microanatomic structures of natural scaffolds. There are many potential materials.[142–146] The biodegraded molecules from polyglycolic acid led to a low pH environment and excited a vigorous inflammatory response when transplanted.[147] Hydrogels also have a slow degradation rate and noncontrolled long-term biologic response.[148]

Recently, a long-segment circumferential trachea along with the carina and the main bronchi was fabricated from a nanocomposite polymer (POSS) covalently bonded to polyurethane (PCU). The casted form was made into the cartilage "U" shaped rings, and the coagulated form was used for the "connective" tracheal part. It was shown to support recipient progenitor cells and was used clinically.[149] Long-term remodeling and outcome remain unknown.

Natural and Decellularized

Natural and decellularized scaffolds are thought to be advantageous because they support adhesion, proliferation, and differentiation of many different cell types.[150] They are composed of extracellular matrix material such as collagens,[42,134,137,151,152] fibrin/hyaluronic acid,[135] and other glycosaminoglycan products. The limitations are their lack of consistency, structure malleability, and biodegradability.

In 2004, a tissue-engineered tracheal patch was used as a bioartificial construct for a tracheal defect in a 58-year-old man.[153] It was composed of autologous muscle, fibroblasts, and a collagen matrix from a decellularized porcine proximal jejunum segment. This scaffold was incubated for 3 weeks in a bioreactor before transplantation. After 12 weeks, the bioartificial patch had a ciliated pseudostratified epithelium and was integrated into the adjacent airway.[153]

In 2008, a 30-year-old woman was the recipient of a decellularized allogeneic trachea for replacement of her left main bronchus. This scaffold required 25 cycles of decellularization based on the absence of major histocompatibility complex markers within the cartilage.[154] The scaffold was then recellularized in a bioreactor with primary autologous epithelial cells and mesenchymal stem cell–derived chondrocytes. The patient did not develop antidonor antibodies and did not receive immunosuppressive therapy. The procedure has since been modified to use the recipient's body as a bioreactor: seeding the scaffold intraoperatively with autologous respiratory epithelial and bone marrow–derived mononuclear cells.[155] This in vivo tissue-engineered approach was used in a case series of 9 pediatric and adult patients with benign and malignant diseases on a compassionate basis. No graft-related mortality was reported after follow-up of 12–42 months, with all bioengineered grafts remaining vascularized and lined with healthy respiratory mucosa. However, partial collapse of the scaffolds was noted in 3 patients.[156,157] The collapse was thought to be due to degradation of the extracellular matrix architecture and a decrease in the mechanical and angiogenic properties that occurs after long-term storage.[158] The group felt that decellularized matrices led to unpredictable results and has since moved on to use an artificial tracheal and bronchial scaffold from a nanocomposite polymeric material.[149]

Bioreactors

Bioreactors are laboratory tissue-culture devices that provide a controllable, mechanically active environment and can be used to study and improve tissue-engineered structures[159] (Figure 3). They enable the cell seeding process, allow for proliferation on a large scale and production of 3D constructs,[160,161] and provide an optimal physiological environment for cell adhesion, growth, and differentiation by provision of flow of nutrient media and mechanical stimulation mimicking conditions of growing organ.[162] Their operational conditions may be manipulated (such as pH, temperature, oxygen tension, and nutrient supply). Several bioreactors have been described for tracheal tissue engineering,[163–167] and a commercial version of this bioreactor launched by Harvard Bioscience currently exists and was used for the first human tissue-engineered tracheal replacement.[154] Following the first clinical transplantation, the authors turned to in situ tissue engineering mentioning long-lasting seeding period, high costs, potential risks of cell differentiation instability, and contamination as bottlenecks to integration of bioreactor-seeded tracheas.[168]

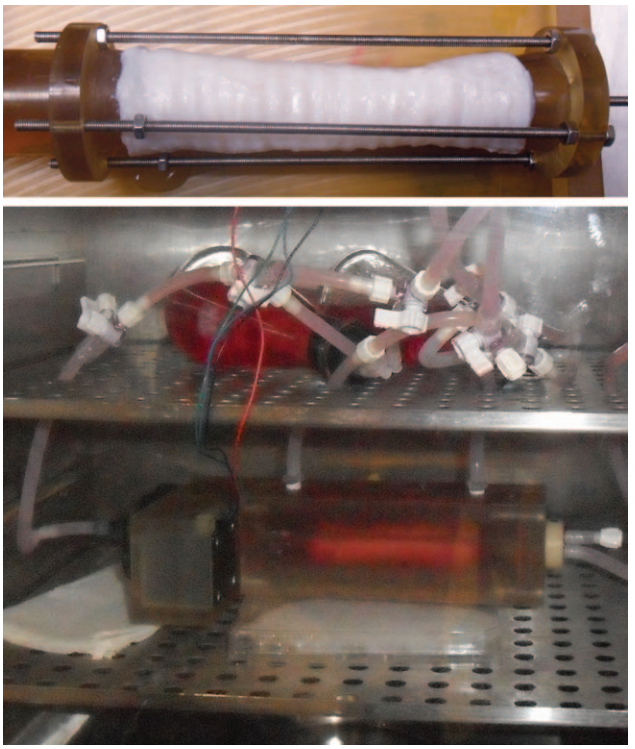

Fig. 3. Decellularized scaffold and bioreactor setup in incubator. Adapted from Haykal S, Salna M, Zhou Y, et al. Double-chamber rotating bioreactor for dynamic perfusion cell seeding of large segment tracheal allografts: comparison to conventional static methods. *Tissue Eng Part C Methods* 2014 Mar 5. [Epub ahead of print].[169] Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

CONCLUSIONS

The anatomical features of the trachea, which include its proximity to major vessels, segmental blood supply, anteroposterior heterogeneity, lateral rigidity, and longitudinal flexibility, make it more complex than a simple conduit. The presence of different tissues, including respiratory epithelium, submucosa, cartilage, and blood vessels, makes reconstruction of the trachea particularly challenging. The attempts that have shown the greatest promise have used tissue-engineered techniques with decellularized allografts. However, there continues to be some significant challenges with biological scaffolds

composed of the extracellular matrix particularly related to revascularization. Plastic and reconstructive microsurgeons can significantly contribute to this field by combining free-flap techniques to allow for initial revascularization of these scaffolds followed by a delayed reconstruction, thus providing a novel technique for reconstruction of circumferential long-segment tracheal defects.

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