

Bioprosthetics and repair of complex aerodigestive defects

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Aerodigestive defects involving the trachea, bronchi and esophagus are a result of prolonged intubation, operative complications, congenital defects, trauma, radiation and neoplastic disease. The vast majority of these defects may be repaired primarily. Rarely, due the size of the defect, underlying complexity, or unfavorable patient characteristics, primary repair is not possible. One alternative to primary repair is bioprosthetic repair. Materials such as acellular dermal matrix and aortic homograft have been used in a variety of applications, including closure of tracheal, bronchial and esophageal defects. Herein, we review the use of bioprosthetics in the repair of aerodigestive defects, along with the unique advantages and disadvantages of these repairs.

Keywords: Bioprosthetic; trachea; aortic homograft; acellular dermal matrix; regenerative medicine



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Introduction

The airway serves as a passive conduit for the passage of air during respiration and a facilitator for clearance of secretions. The esophagus, on the other hand, is an active conduit for oropharyngeal sections and food particulate. Both of these hollow organs travel in close anatomic proximity throughout the chest and are separated only by a thin layer of connective tissue. Any injury or disease affecting one or both can lead to a loss of domain and result in connection of the two lumens. Such a fistulous connection inevitably leads to airway contamination with secretions, food and possibly gastric secretions, in the setting of gastroesophageal reflux. Ideally, repair of either organ restores their integrity and their basic functions. Primary repair is the preferred method for correction of defects to the aerodigestive track. In cases of substantial tissue loss or stenosis, circumferential resection and subsequent reconstruction may be necessary. Through a variety of techniques, including neck flexion, laryngeal release, airway mobilization and hilar release, tracheal defects of up to 5 cm may be closed primarily in the ideal patient (1). Similarly, large esophageal defects may be repaired through resection and repair either with or without

gastric or colonic conduits. A key element of the successful repair of aerodigestive fistula is the interposition of robust vascularized tissue (2). It has become an exceptionally rare circumstance in which primary repair of a tracheal defect is not possible and is generally associated with rare neoplastic diseases such as adenoid cystic carcinoma (3,4). After reviewing our institution's experience over an 8-year period, we found only 8 instances out of 342 airway procedures in which an alternative to primary repair or permanent tracheostomy was required (5).

In scenarios in which primary repair is not an option, one alternative is the use of bioprosthetic material. These materials are derived from cadavers and treated chemically and physically to remove cells and other immunologically reactive tissue. Compared to traditional synthetic prosthesis, bioprosthesis have several advantages, including improved handling, minimal immunogenic response and potentially decreased risk of bacterial seeding and infection due to a high degree of biocompatibility, especially in the absence of crosslinking. Herein, we will focus on the current state of bioprosthetic repair of tracheal, bronchial and esophageal defects. We will include bioprosthetic repairs in which the defect was limited to either the airway or the esophagus, as well as repairs involving aerodigestive

fistulas. Other methods of repair, such as tracheal transplantation, autologous reconstruction and tissue engineering approaches represent potential alternatives (6,7), but are beyond the scope of this current review.

Bioprosthetic materials

Bioprosthetic materials are derived from cadaveric tissue through chemical treatment, freezing, or lyophilization to remove or denature immunologically reactive cellular components and to eliminate any possible pathogens. The remaining extra-cellular matrix can then serve as a scaffold for tissue ingrowth while functioning as an airtight seal for the repaired defect. While there is evidence that some bioprosthetics may retain active chemoattractants, binding sites and growth factors within the preserved extra-cellular matrix, these factors do not elicit acute rejection of the graft and do not necessitate immunosuppressive treatments (8). Additionally, bioprosthetics have a potential advantage compared to traditional prosthetic materials through theoretic resistance to bacterial and fungal colonization, which can doom any repair. Given the constant exposure of the airway and esophagus to oral flora and the atmosphere with its associated pathogens, resistance to infection is a unique requirement to aerodigestive repair. To date, the most common materials used in the bioprosthetic repair of aerodigestive defects are aortic homograft and acellular dermal matrix.

Acellular dermal matrix

Acellular dermal matrix came into use in the 1990s and was first used for treatment and temporary coverage of full thickness burns (9,10). Over the past two decades it has been adopted with varying success in a variety of applications including abdominal wall reconstruction, breast reconstruction and repair of pharyngeal defects (8,11). In 2006, Bozuk *et al.* reported the repair of an esophageal defect with acellular dermal matrix (12) and in 2008 Su *et al.* reported the use of acellular dermal matrix in the repair of the trachea in a patient who presented with a large tracheoesophageal fistula (13). Acellular dermal matrix is commercially available from human and animal sources in various sizes and thicknesses. It is harvested from cadavers and undergoes processing that removes donor cells, but leaves the extracellular matrix intact. This processing eliminates the need for post-implantation

immunosuppression. Depending on packaging, it may require rinsing and/or rehydration in saline at time of implantation.

Aortic homograft

Aortic homografts, also sometimes referred to as allografts, have been used clinically in aortic valve replacement and in arch repair since the 1960s (14,15). Experimentally, aortic homografts were first used in tracheal repair in a canine model by Pressman and Simon in 1959 (16). During that same time period, two case reports emerged regarding the use of aortic homograft as a circumferential conduit in esophageal repair. However, information regarding these repairs is scarce and will not be further explored in this review (17). The first report of clinical use in airway repair was in 1999 by Chahine *et al.* and is discussed in the following section (18). Grafts are harvested from cadaveric donors, disinfected and packaged in a cryopreservation solution in which they can be stored for 10 years. They are commercially available and can be used off the shelf within 30 minutes of opening. The graft is thawed and rinsed prior to implantation. The graft may be perforated with a 16-gauge needle prior to implantation to encourage tissue ingrowth without compromise to the airtight competency of the repair. Given the method of disinfection and cryopreservation, most of the immunoreactive components of the donor are removed and there is no reported risk of rejection or need for post-operative immunosuppression.

Other bioprosthetics

Aortic homograft and acellular dermal matrix are the only bioprosthetics currently used in clinical practice in the repair of large airway defects. Experimental work using canine models and freeze-dried tracheal homografts was performed by several investigators in the 1950s and 1960s, but abandoned due to development of stenosis and necrosis of the graft (19,20). In the 1990s, clinical attempts were made using tracheal homografts in a pediatric population to treat long segment tracheal stenosis; however, frequent use of stents was required and many patients required serial bronchoscopy and debridement due to development of excessive granulation tissue (21,22). Due to these difficulties and a lack of commercial availability, tracheal homografts have largely been abandoned, with an exception reserved for tissue engineering approaches which are beyond the scope of this review.

Pre-operative concerns

In the unique event that a patient cannot tolerate a primary repair and bioprosthetic repair is being considered, optimization prior to any intervention is critical. Patients should be referred to a high-volume center for evaluation by a surgical team experienced in complex airway repair. Functional status should be carefully assessed to determine likelihood of complications and post-operative recovery. Prognosis should be addressed and overall goals of the procedure established, especially in patients suffering from neoplastic disease. Principles of aerodigestive fistula repair such as interposition of viable tissue, preoperative clearance of pulmonary infections and postoperative extubation apply. While bioprosthetics are theoretically resistant to bacterial seeding, they represent a non-vascularized foreign body until fully incorporated and are thus at risk for colonization. Temporization with tracheostomy, stenting, or T tube to allow for treatment of underlying infection is preferable over placement of a bioprosthetic into a contaminated field.

Clinical use

Over the past 20 years, 29 patients have undergone bioprosthetic repair for complex tracheal, bronchial, or esophageal defects, including 9 with aerodigestive fistulas. Of those 29 patients, 10 underwent repair with acellular dermal matrix (*Table 1*), while the remaining 19 underwent repair with aortic homograft (*Table 2*). In those repaired with acellular dermal matrix, the underlying pathology included leaks after esophagectomy, primary malignancy, post-intubation injury and AIDS associated esophagitis (5,12,13,23-26). Acellular dermal matrix was used in the repair of the airway in six cases and repair of the esophagus in four cases. In patch repair of the airway and the esophagus, acellular dermal matrix proved reliable with relatively minimal post-operative complications. These were generally limited to benign stricture or excessive granulation tissue development, which was managed non-operatively with serial dilation or debridement respectively. In the single patient with a circumferential repair, significant complications were encountered, including graft slippage requiring reoperation and prolonged tracheostomy (26).

In patients who underwent treatment with aortic homograft, bioprosthetic repair was limited to the trachea and bronchus (5,18,27-31). The underlying pathology within this group was more heterogeneous than that of patients repaired with acellular dermal matrix and included

a substantial percent with tracheal neoplastic disease (42%). As in those patients treated with acellular dermal matrix, aortic homograft patch repair was successful with complications limited primarily to excessive formation of granulation tissue and stenoses that could be treated bronchoscopically. In contrast to patients treated with acellular dermal matrix, 11 patients underwent a circumferential or near circumferential repair with a tubularized graft composed of aortic homograft. In the majority of these cases, prolonged stenting of several months to years was required. In addition, more frequent and severe complications were encountered, including graft migration, anastomotic dehiscence and sternal dehiscence, all of which required reoperation. The use of an interpositional graft composed of aortic homograft was used only for temporization in one patient until redo lung transplantation could be performed three days later (27). As a result, there are only 10 patients who underwent interpositional bioprosthetic repair with post-operative follow-up beyond a few days.

With regards to use as a patch, both bioprosthetics provide an airtight closure with minimal significant complications. In this function, acellular dermal matrix and aortic homograft represent a viable option for the management of aerodigestive defects that, either due to size or complexity, exceed the limits of a standard primary repair. Given the complexity of these procedures, it is prudent to buttress any repair with healthy vascularized tissue. While select cases may exist in which buttressing can be omitted in simple primary repair (32), in the complicated cases described above it is preferable to use healthy, vascularized tissue to support the bioprosthesis, prevent malacia and provide protection in case of a leak. Indeed, in only four instances has an attempt at repairing the airway without an accompanying buttress been reported. In these four patients, two died within 1 month and a third underwent excision of the graft and repeat lung transplantation after only three days (5,18,27,28).

Circumferential or near circumferential repair with a tubular interpositional graft is a major challenge in surgery of the airway. Attempts at repair with acellular dermal matrix and early attempts with aortic homograft failed secondary to graft migration and dehiscence (26,28). Later circumferential repairs with aortic homograft or fresh allograft have been more successful and benefited from the use of long-term stenting (29,31). The most recent work reported by Martinod *et al.* is promising, with long-term follow-up demonstrating a stable repair even after

Studies	Year	Patients (n)	Defect(s)	Type of repair	Buttress	Major complication(s) and further intervention(s)	Airway and enteric function
Bozuk <i>et al.</i> (12)	2006	1	Anastomotic leak after Ivor-Lewis esophagectomy	Patch repair of esophagus	None	Small ulceration at anastomosis did not require further treatment	Resumed oral diet with supplemental tube feeds, no tracheostomy requirement
Su <i>et al.</i> (13)	2008	1	TEF after prolonged intubation	Patch repair of trachea	Pectoralis major	None	Decannulated and resumed oral diet
Morse (23)	2009	1	Bronchial esophageal fistula in patient with AIDS associated esophagitis	Patch repair of bronchus	Latissimus dorsi	Multiple debridements of granulation tissue	Resumed oral diet, no tracheostomy requirement
Reames and Lin (24)	2013	1	Bronchogastric fistula after 3-hole esophagectomy	Patch repair of bronchus	Intercostal muscle	None	Resumed oral feeds, no tracheostomy requirement
Thomas <i>et al.</i> (25)	2014	3	Anastomotic leak after Ivor-Lewis esophagectomy	Patch repair of esophagus	None	Temporary post-operative stenting, stricture requiring serial dilation	Resumed oral diet, no tracheostomy requirement
			Anastomotic leak after Ivor-Lewis esophagectomy	Patch repair of esophagus	None	Temporary post-operative stenting, stricture requiring serial dilation	Resumed oral diet, no tracheostomy requirement
			Anastomotic leak after Ivor-Lewis esophagectomy	Patch repair of esophagus	None	Temporary post-operative stenting, pseudodiverticulum at patch that did not require further intervention	Resumed oral diet, no tracheostomy requirement
Udelsman <i>et al.</i> (5)	2016	2	TEF associated with esophageal squamous cell carcinoma and esophageal stent erosion	Patch repair of trachea	None	None	Decannulated and resumed oral diet
			TEF associated with esophageal squamous cell carcinoma and esophageal stent erosion	Patch repair of bronchus	Latissimus dorsi, intercostal muscle	None	Tracheostomy dependent, resumed oral diet
Bolton <i>et al.</i> (26)	2017	1	TEF associated with Hodgkin's lymphoma	Tubular tracheal conduit	Latissimus dorsi, sternocleidomastoid	Graft slippage and redo of anastomosis, recurrent stricture requiring serial dilation, recurrent pneumonia	Required laryngectomy and further reconstruction as well as esophageal reconstruction with colonic interposition, eventually decannulated and resumed oral diet

[†], Udelsman *et al.* reports 3 patients who underwent repair with acellular dermal matrix; however, one was previously reported in case report by Morse and is included only under that heading. TEF, tracheoesophageal fistula.

Table 2 Aortic homograft in repair of tracheal, bronchial, and esophageal defects

Studies	Year	Patients (n)	Defect(s)	Type of repair	Buttress	Major complication(s) and further intervention(s)	Airway and enteric function	Defect(s)
Chahine <i>et al.</i> (18)	1999	3	Breakdown of anastomosis after double lung transplantation and balloon dilation	Patch repair of bronchus	None	Died at 1 month from unrelated causes	–	Breakdown of anastomosis after double lung transplantation and balloon dilation
			Gun shot wound	Patch repair of bronchus	Pericardial fat pad	None	No tracheostomy requirement, resumed oral diet	Gun shot wound
			Tracheoesophageal fistula after prolonged intubation	Patch repair of trachea	Intercostal muscle	Stenosis of esophageal repair requiring serial dilation	No tracheostomy requirement, diet unknown	Tracheoesophageal fistula after prolonged intubation
Hoffman <i>et al.</i> (27)	2001	1	Tracheal dehiscence after heart-lung transplant	Interposition graft	None	Retransplant and resection of graft on post-operative day 3	–	Tracheal dehiscence after heart-lung transplant
Davidson <i>et al.</i> (28)	2009	1	Dehiscence after tracheal resection and reconstruction	Interposition graft with Montgomery tube	None	Proximal dehiscence, mediastinitis, and death	–	Dehiscence after tracheal resection and reconstruction
Wurtz <i>et al.</i> (29)	2010	6	Tracheal defect after resection of MEC	Interpositional graft with silicon stent [†]	Pectoralis major	Dehiscence of proximal anastomosis requiring repair, sternal dehiscence, stent dependent	No tracheostomy requirement	Tracheal defect after resection of MEC
			Tracheal defect after resection of ACC	Interpositional graft with silicon stent [†]	Pectoralis major	Anterior spinal cord ischemia, additional bronchial stenting	No tracheostomy requirement,	Tracheal defect after resection of ACC
			Tracheal defect after resection of ACC	Interpositional graft with silicon stent	Pectoralis major	Pneumonia, stent dependent	No tracheostomy requirement	Tracheal defect after resection of ACC
			Tracheal defect after resection of ACC	Interpositional graft with silicon stent	Pectoralis major	Fungal infection of graft requiring replacement, TEF, stent dependent	Tracheostomy dependent	Tracheal defect after resection of ACC
			Tracheal defect after resection of ACC	Interpositional graft with silicon stent	Pectoralis major, thymopericardial flap	Sternal dehiscence	No tracheostomy requirement	Tracheal defect after resection of ACC
			Tracheal defect after resection of ACC	Interpositional graft with silicon stent	Pectoralis major, thymopericardial flap	None, stent dependent	No tracheostomy requirement	Tracheal defect after resection of ACC

Table 2 (continued)

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Studies	Year	Patients (n)	Defect(s)	Type of repair	Buttress	Major complication(s) and further intervention(s)	Airway and enteric function
Martinod <i>et al.</i> (30)	2011	1	Bronchial defect after resection for NSCLC	Interpositional graft with nitinol stent	Latissimus dorsi	Stent dependent	No tracheostomy requirement, resumed oral diet
Udelsman <i>et al.</i> (5)	2016	5	Tracheo-gastric fistula after esophagectomy and reconstruction	Patch repair of trachea	Omentum	Debridement of granulation tissue	Tracheostomy and tube feed dependent
			Mesh erosion after repair of tracheomalacia	Patch repair of trachea	Polypropylene mesh	None	No tracheostomy requirement, resumed oral diet
			TEF after prolonged intubation	Patch repair of trachea	Omentum	None	Remained tracheostomy and tube feed dependent [§]
Martinod <i>et al.</i> (31)	2017	2	Dehiscence after tracheal resection and reconstruction	Patch repair of trachea	Strap muscle	Stricture requiring balloon dilation	Initially tracheostomy dependent with subsequent decannulation
			Tracheal defect after resection of ACC	Patch repair of trachea	Latissimus dorsi, intercostal muscle	None	No tracheostomy requirement, resumed oral diet
			Laryngotracheal stenosis after prolonged intubation	Interpositional graft with nitinol stent with preservation of membranous wall	Strap muscle	Prolonged stent requirement with removal at 15 months	Temporary tracheostomy with subsequent decannulation, resumed oral diet
Martinod <i>et al.</i> (31)	2017	2	Laryngotracheal stenosis after prolonged intubation	Interpositional graft with nitinol stent with preservation of membranous wall	Strap muscle	Prolonged stent requirement with removal at 39 months, debridement of granulation tissue	Temporary tracheostomy with subsequent decannulation, resumed oral diet
			Laryngotracheal stenosis after prolonged intubation	Interpositional graft with nitinol stent with preservation of membranous wall	Strap muscle	Prolonged stent requirement with removal at 39 months, debridement of granulation tissue	Temporary tracheostomy with subsequent decannulation, resumed oral diet

stent removal in patients undergoing reconstruction for benign laryngotracheal stenosis. It remains to be seen if the robustness of the repair is maintained in the challenging situation of underlying malignancy or concomitant enteric fistula.

Finally, the exact mechanisms through which bioprosthetics aid in the repair of aerodigestive defects requires further investigation. In the majority of studies in which the bioprosthetic repair has been tracked through long-term follow up, “healing” occurs with deposition of granulation tissue, contraction and scarring (5,29). This process highlights the need for frequent bronchoscopic surveillance with debridement and balloon dilation if needed. At no point in previous reports has there been substantive evidence of cartilage formation. However in their recent follow up of two patients with near circumferential aortic homograft repair, Martinod *et al.* report the development of cartilage derived from recipient cell lines. They propose a mechanism of “*in vivo* tissue engineering”, in which remaining donor cells within the extracellular matrix release proangiogenic, chemoattractants and growth factors which stimulate repopulation of the graft with recipient progenitor cells. They attribute the success of their work in part to storage of cryopreserved aortic grafts at -80°C rather than -150°C , which they report helps preserve donor growth factors and protected cells within the extracellular matrix (31). However, several questions regarding this repair remain unanswered, including how the graft becomes revascularized and the mechanistic pathway by which growth factors orchestrate the complex migration and differentiation of circulating host cells.

Conclusions

Major advances in airway surgery during the 20th century have made the vast majority of aerodigestive defects amenable to primary repair. In the last 20 years, bioprosthetic repairs has emerged as an alternative in rare cases in which primary repair is not an option. The decision to forgo primary repair and elect for bioprosthetic repair should only be made after careful review at a center experienced in complex airway surgery.

Both acellular dermal matrix and aortic homograft have been tested in numerous settings as a patch repair. When used in conjunction with a healthy well vascularized buttress, these bioprosthetics provide a durable airtight seal preserving the competency of the airway and allow for a natural healing process to occur. In the case of

anastomotic leak involving the esophagus or a gastric conduit, acellular dermal matrix has also provided a competent repair and spared patients further resection and reconstruction. In addition to these successful patch repairs of the trachea, bronchus and esophagus described above, aortic homograft has been used in the reconstruction of the larynx after partial laryngectomy in a series of 15 patients with neoplastic disease reported by Zeitels *et al.* As in the trachea, these bioprosthetic repairs of the larynx allowed the majority of patients to achieve decannulation, preserve phonation and resume an oral diet (33). While the focus of this review is on the repair of defects involving the trachea, bronchus and esophagus, the laryngeal repairs reported by Zeitels *et al.*, along with the work by Sinha *et al.* describing aortic homograft reconstruction of the pharynx, demonstrate both the versatility and robustness of bioprosthetics when used in patch repair and with a tissue buttress (11).

The more difficult situation of circumferential airway repair is under continuous investigation. Multiple proposed repair modalities have been explored, including transplantation, tissue engineering and as discussed above, bioprosthetic repair. However, the results of aortic homograft repair with longstanding airway stenting by Martinod *et al.* are encouraging (31).

In regards to future use of bioprosthetics, both as patches and circumferential interpositional conduits, several questions persist. First, it remains to be seen whether a bioprosthetic repair can withstand the additional burden of adjuvant chemotherapy and radiotherapy in patients with malignant neoplastic disease. Furthermore, when a patch repair is planned in a patient with neoplastic disease, diligence must be taken to ensure adequate resection and negative margins. It may be a challenge to balance adequate oncologic resection while leaving enough native tissue to facilitate bioprosthetic repair. Moreover, the role of bioprosthetic repair in a palliative setting when complete resection is not possible remains undetermined. Lastly, the role for bioprosthetics in a still growing pediatric population is unclear. Chahine *et al.* have reported successful patch repair using aortic homograft in two pediatric patients with minimal morbidity at 2-year follow up (18); however, the growth potential of a repair with these materials remains to be examined, especially if used as a tubular interpositional graft is uncertain. These questions will quickly develop clinical relevancy as bioprosthetics become a more accepted treatment option for complex patients with defects unsuitable for primary repair.

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Footnote

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