Review Article

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

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Abstract: The patient population in desperate need for an airway substitute are individuals with long segment tracheal defects that are considered, technically, inoperable. Regardless of the underlying etiology, benign or malignant growing processes, this patient category enters a palliative setting or require tracheal transplantation. Different airway substitutes have been categorized by Grillo as follows; tracheal transplantation, autogenous tissue, non-viable tissue, tissue-engineering and foreign materials. These fields have been explored in the past in animal models and in clinical patients. Research on airway replacement has been exposed to a level of controversies in the past years. The field has been turbulent and apocryphal. In particular, the area of tissue-engineering using stem cells has suffered from a major set-back leaving scientists, clinicians and ethical committees skeptical. Recently, a hopeful study emerged using aortic allografts as tracheal substitutes in patients with airway defects. The initial results seem promising and reliable. The developments of the field at this point seem striking and hopeful. The focus of this review is to shed light on developments in the field of aortic allografts as substitute for tracheal replacement.

Keywords: Tracheal stenosis; airway substitutes; aortic allograft; tissue-engineering

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Introduction

The correlation of airway structure and function was first elucidated by Leonardo da Vinci. Early drawings demonstrate the anatomy of the uvula, larynx, vocal cords and the airway tree. In fact, much ahead of his time, Da Vinci came up with "the Da Vinci rule" where he elaborated upon his understanding of the cross-sectional area of the airway and tree branching. He proposed that the sum of the cross-sectional area of all tree branches above a branching point equals the cross-sectional area of the trunk or the branch immediately below the branching point (1,2). These studies have been revisited at Princeton University recently. In his early documents da Vinci mentions "*the voice becomes weak in elderly because all the passages of the trachea are narrowed, in the same manner as the other entrails*". Although some assumptions of this Renaissance man were speculative, the concept of "structure and function" and the direct correlation of tissue and an accompanying purpose was emphasized repetitively in his work. The modern understanding of tracheal structure and function states an anatomical tubular structure containing cartilage to provide rigidity, intercartilagenous muscular area allowing longitudinal flexibility, dorsally muscular wall permitting esophageal motility and epithelialized inner lining necessary for clearance of the inner airway surface. The field of airway substitute generation attempts to recapitulate these attributes. However, this endeavor has appeared far from simple with various fields facing dilemma's in one or more of these facets.

Tracheal allotransplantation as an ultimate solution for long-segment airway defects is pioneered by Delaere *et al.* (3) at Leuven Hospital. The main challenges faced in tracheal allotransplantation remain blood supply to the donor and the use of immunosuppressive therapy. Initial reports of non-vascularized tracheal transplantation without immunosuppressive therapy date back many years and did not seem to be successful or clinically applicable for over 20 years (4,5). The very first viable case of tracheal transplant took advantage of autogenous omentum as a vascular bed for the allotransplant. The transplant remained viable for at least 60 days (6). Since 2010 Delaere *et al.* (7-9) have repetitive reports of vascularized tracheal allotransplants. The trachea is heterotopically placed in the forearm where the fascia flap pedicles around the transplant thereby creating a vascular network. The trachea is then re-transplanted orthotopically in the airway position. The first series of patients undergoing allogenic tracheal transplantation reports from 2016 where patients with long-segment tracheal stenosis were treated successfully (10). The main hurdle in allogenic transplantation remains the initial requirement of immunosuppressive therapy until the transplant is vascularized. In patients with malignant growing tumors this phase may be detrimental for the oncologic prognosis. The concept of autogenous tissue reconstruction is based on the notion of creating a tubular structure that can sustain viable, using a vascularized pedicle and remain open through stent placement or cartilage transplantation. Many autogenous tissue sources have been applied previously (11-14) The largest series of 12 patients with 8 years follow-up using radial fasciocutaneous flap with subsequent cartilage transplantation and stent placement was reported in 2013 (13). Although a novel approach, in a number of patients this approach was complicated by respiratory stress and tracheostoma dependency. The latter due to a lack of inner lining epithelium that failed to regenerate in this setting. An additional layer of complexity was introduced to this concept by separately transplanting oral mucosa in an attempt to overcome the ciliary dysfunction (12). This final step introduces a new level of surgical complexity and procedure duration with local complications.

Like in other fields, tissue-engineering of the trachea is based on the notion of isolating stem cells, seeding a scaffold, generation of new formed tissues of interest and reimplantation into the patients. Given the straightforward structure of the trachea, tissue-engineering of the trachea has been underestimated over and over again. In 2008, the field was optimistic and hopeful by the publication of the first clinical application of tissue-engineering by Macchiarini *et al.* A decellularized tracheal was used as a scaffold. Mesenchymal stem cells derived from bone marrow of the recipient, 30-year-old woman, were seeded on the scaffold and transplanted into the patient. The results reported a better quality of life and regeneration of a biomechanical functional airway (15). The developments seemed to evolve based on a second publication in 2011 where the airway of a 36-year-old patient was replaced using a bioartificial scaffold seeded with bone-marrow mononuclear cells after a 36-hour incubation in a bioreactor. Postoperatively, the patient was given EPO and granulocyte colony-stimulating factor (16). In 2014 a 5-year follow-up study of the initial transplantation was reported where the results seemed promising, the graft appeared open despite a proximal stenosis the site of anastomosis (17). Unfortunately, in 2016 news of misconduct emerged and false reporting of the severity of complications and number of dead patients was reported. Martinod *et al.* presented a case of tissue-engineered tracheal transplantation in a pediatric patient where decellularized scaffolds were seeded with bone marrow stromal cells and covered with mucosal epithelium. Unfortunately, vascularization of the substitute was suboptimal due to scarcity of omental tissue. This patient suffered from respiratory arrest in the second week after transplantation and died. So far, there is 1 case of a successful treatment using tissue-engineered trachea. Hamilton *et al.* treated a pediatric patient with a severe airway defect, repetitive stent placement and bronchoscopic procedures. Tracheal transplant was seeded with bone-marrow cells and treated with TGF-β, EPO and granulocyte colony stimulating factor. Despite a substantial lack of mechanistic evidence for regeneration using cells as such and these particular growth factors, the graft seems patent at 4 years with possible epithelial regeneration (18).

Recently, perhaps a paradigm shifting, single-center, prospective study emerged (19). In an enrollment of 6.5 years, 13 patients suffering from severe tracheal defects or proximal lung tumors requiring a pneumonectomy were selected for airway transplantation upon radical resection of the primary lesion. The substitute is a cryopreserved aortic allograft. The surgical technique used was the principle resection technique and primary re-anastomosis. Bronchoscopic 3D imaging was used to develop custom made stents to allow graft patency for the initial phase to prevent airway collapse. The stents were then removed at roughly 18 months post-transplantation. Histologic

analysis from post-transplantation biopsies, 15 months, after transplantation reveal potential regeneration of collagen and ciliated epithelium. The 90-day mortality rate was 5% due to death of 1 patient with carinal transplantation. Major post-operative morbidity occurred in 4 patients and included laryngeal edema, pulmonary edema, acute respiratory stress syndrome and atrial fibrillation. At 3 years, 76.9% of patients were alive. Of these 10 patients 80% had normal breathing pattern and functionally formed airway after stent removal. These finding and reports seem reliable and promising. However, the current trial in is not the first clinical application of aortic allografts as tracheal substitute. In 2006, Wurtz *et al.* reported tracheal replacement in 2 patients with chemotherapy and radiotherapy resistant tumors in 2006. Aortic allografts accompanied by silicon stents were placed in the tracheal position. Although the first patient had an uneventful course, the second patient developed spinal cord injury. A complication not well understood but extremely debilitating (20). Other sporadic cases of clinical application have been reported (21,22).

A glimpse at the literature reveals that this clinical trial is based on years of experience in animal models using aortic allografts as airway substitutes. The concept of using the aorta as a tracheal substitute is based on the facts that the aortic tissue is well-known for its solidity, compliance and resilience to infection (23). The major disadvantage being the propensity towards collapse which can be overcome using stents. The animal studies conducted by Martinod *et al.* revealed no severe adverse effects up to 3 years and demonstrated signs of airway regeneration upon time. In the study by Makris *et al.*, cryopreserved aortic allograft transplantation in minipigs showed signs of transformation of the graft into a chimeric conduit sharing attributes of aortic tissue as well as tracheal tissue [Makris *et al.* 2010 (24)]. Kim *et al.* performed tracheal replacement using aortic allografts with stenting and demonstrated stent migration in 8 out of 12 dogs. Regeneration of mature cartilage ring did not seem to occur making prolonged stenting mandatory (25). Fresh aortic allograft transplantation in one study failed to show signs of cartilage regeneration in sheep. Instead much connective tissue and fibrosis was detected with subsequent graft shortening (22).

To address the question of regeneration and mechanism of regeneration in animal subjects, the Martinod group performed an interesting study where the aorta of a male sheep was transplanted as a trachea of a female sheep. Upon time, histologic specimens were analyzed for presence of the SRY gene in the newly formed cartilage. The SRY gene was present in the male sheep but not in the female sheep indicating that the newly formed cartilage is driven off the patient's own native cells.

To further elucidate the mechanism of regeneration and cell source for neo-cartilage formation, authors went back to a rabbit model. Since chondrocytes do not perform chemotaxis in nature, the assumption of neo-cartilage formation through circulating mesenchymal stem cells emerged. This finding was elaborated upon in a rabbit model (26). Rabbits underwent tracheal replacement using aortic allografts. One group of rabbits was given fluorescent tagged mesenchymal cells. Immature disorganized cartilage formation was considered to have developed from these fluorescent tagged cells. Thus, an innate bone marrow response may be available in regeneration of the neo-trachea.

Conclusions

So far, the field of neo-trachea formation has been anything but stagnant. Long segment tracheal defects remain a major clinical problem and requires remedy. It is noteworthy that the current therapeutic approaches evolve around combining of knowledge, experience and technical expertise. From tracheal transplantation to isolation of progenitor cells, development of scaffolds, using stents etc. Until now, the only tracheal substitute in clinical setting without major adverse effects seem to arise from the group of Martinod. A few aspects from this recent trial are remarkable and worth pointing out. Firstly, the patients do not suffer from any immunogenic adverse effects of an allogenic aortic transplant. Empirically aortic allografts in the aortic position have lost popularity due to accelerated degeneration and calcification of the grafts, presumably due to an immunogenic response. Yet, this matter does not seem to be a hurdle in the tracheal position. Based on the experiments and now clinical data, at least in one group's hands, Martinod *et al.*, the aortic allograft seems an ideal scaffold where regeneration occurs, probably, in a bone- marrow mesenchymal stem cell-derived fashion. 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.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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