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Research review

Large animal models for long-segment tracheal reconstruction: a systematic review

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ABSTRACT

Background: The reconstruction of extensive tracheal defects is an unresolved problem. Despite decades of research, a reliable and practical substitute remains to be found. While there have been clinical reports of successful long-segment tracheal reconstruction, reproducibility and widespread applicability of these techniques have yet to be achieved. Large animals such as the dog, pig, sheep, and goat have comparable tracheal morphology and physiology to humans making them useful preclinical models to screen potential therapeutic strategies.

Materials and methods: The literature was reviewed to identify large animal models commonly used for tracheal reconstruction. A systematic search of PubMed and EMBASE was performed for large animal studies reporting on the reconstruction of long-segment tracheal and carinal defects. Fifty-seven studies were identified for analysis.

Results: There is no standard large animal model available for tracheal research. In recent years, livestock species have gained favor over dogs as animal models in this field. The minimum requirements for successful tracheal replacement are rigidity, vascularity, and epithelial lining. Early attempts with synthetic prostheses were met with disappointing results. An autologous tracheal substitute is ideal but hindered by limited donor site availability and the lack of a dominant vascular pedicle for microsurgical reconstruction. Although tracheal allotransplantation enables like-for-like replacement, there are unresolved issues relating to graft vascularity, immunosuppression, and graft preservation. Tissue engineering holds great promise; however, the optimal combination of scaffold, cells, and culture conditions is still indeterminate.

Conclusions: Despite impressive advances in tracheal reconstruction, a durable substitute for extended tracheal defects continues to be elusive.

Introduction

Tracheal disease is an uncommon but important clinical problem. Its function is easily compromised by neoplasms, traumatic injury, and congenital disorders, which result in stenosis or tracheomalacia affecting quality of life and survival. Primary tracheal tumors represent about 0.1% to 0.4% of all newly diagnosed cancers or 2.6 cases per million per year.[1]

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The true incidence of congenital tracheal stenosis, a rare disorder that often leads to severe respiratory insufficiency, is unknown as many infants die before the diagnosis is made.[2] Severe post-tracheostomy and postintubation tracheal stenosis are also uncommon entities with an estimated incidence of 4.9 cases per million per year.[3] Management of these conditions in specialized units is ideal as their low incidence results in few centers accumulating sufficient meaningful experience to ensure optimal outcomes.

Although tracheal stenosis and malignant strictures may be treated by balloon dilatation and stent or T-tube implantation, stent-related complications and recurrent stenosis are common. Long-segment congenital tracheal stenosis can now be effectively managed by slide tracheoplasty, however, subsequent tracheal dilatation and stenting are often still required.[4] Surgical resection remains the only definitive treatment for tracheal malignancy and tracheobronchial stenosis. Primary end-to-end anastomosis can be achieved if the affected segment does not exceed half the entire tracheal length in adults or one-third in children.[5] The maximal resectable tracheal length is constrained by tension at the anastomosis. Lengthier lesions not amenable to resection and primary repair are thus managed palliatively with increased morbidity and mortality. To date, functional tracheal reconstruction remains a true surgical challenge. While many studies have reported successful reconstruction of partial or short-segment defects, replacement of long circumferential tracheal lesions has been problematic due to the lack of satisfactory tracheal substitutes.

The trachea, a seemingly simple conduit for gaseous exchange, is structurally difficult to replicate. It provides a semirigid yet flexible and airtight airway lined with vascularized epithelium that acts as a barrier to the external environment. Normal tracheal mucociliary clearance is key in preventing the accumulation of secretions and resisting bacterial colonization. Thus, the ideal tracheal substitute should be laterally rigid yet longitudinally flexible with an airtight lumen and an internal lining of ciliated respiratory epithelium. It must also be biocompatible, nontoxic, nonimmunogenic, noncarcinogenic and resist dislocation, erosion, and stenosis over time.[6] Freedom from the need for immunosuppression and ease of implantation are further desirable features.

Animal models have been instrumental in the study of airway disease and are indispensable in translational research. Rodent models have been used extensively in tracheal studies to improve the understanding of basic concepts and to develop new therapeutic strategies. In contrast, the niche for large animals lies in validating the practicality and clinical applicability of newfound tracheal substitutes. Compared to smaller-sized animals, the airway structure of larger mammals such as the dog, pig, sheep, and goat is more similar to that of humans in terms of size, morphology, and physiology.[7,8] They remain the best testing ground to ensure that subsequent studies in humans are ethically pursued. Although animal experiments may be poor predictors of the human response to a proposed treatment,[9] tragedies such as the scandal at Karolinska Institute emphasize the importance of large animal model efficacy testing before the launch of any clinical trial.[10] All human research studies should be subjected to approval by regulatory boards such as the Institutional Review Board to safeguard the interests of study subjects and preserve the credibility of trial results so that future patients may be treated optimally.

Several approaches to tracheal reconstruction have already been trialed in clinical practice and these are summarized in other reviews.[11,12] Successful reports of large defect reconstruction comprise mainly of case reports and small case series with limited data on long-term outcomes. Not infrequently, reintervention was required to maintain airway patency. Further preclinical studies are required to refine many techniques and to explore treatment strategies that can be widely applied in the clinical setting.

The aim of this article is to provide an overview of large animal models that have been commonly used in tracheal replacement studies. To guide future research in this area, recent approaches to long-segment tracheal reconstruction in these animals are also systematically reviewed and summarized.

Materials and methods

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, a systematic search of PubMed and EMBASE was conducted on August 10, 2017, to identify large animal studies published in English during or after 1990. Search terms were focused on “tracheal reconstruction” and “animal model trachea.” Each study was verified for its relevance to the topic, specifically the reconstruction of long-segment tracheal defects. “Long-segment defects” were defined as those measuring 4.5 cm or greater as defects above this length required additional mobilization of surrounding tissues to achieve end-to-end anastomosis within safe tension limits in humans.[13] Studies on carinal reconstruction were also included as the repair of carinal defects by primary anastomosis is often complicated by dehiscence due to high tension.[14] Citations referenced in short-listed articles were also reviewed to identify other relevant studies. The search protocol and reasons for exclusion are depicted in the flow chart in Figure. A total of 57 articles were selected for review. Their details are summarized in Table 1.

Results

Large animals in biomedical research

At present, there is no standard large animal model available to screen candidate tracheal replacement strategies for clinical application. Historically, dogs were favored in biomedical research due to their availability, size, ease of use, and similarity to humans in terms of anatomy and physiology.[71] Thus, many earlier studies in tracheal research were performed using canine models (Table 1). However, their use has declined over time due to ethical concerns and societal pressures to avoid the use of domesticated animals.[72]

In their place, livestock species such as pigs, sheep, and goats are becoming an increasingly popular bridge between traditional small animal models and human research. Surgery, tissue recovery, serial biopsies and blood sampling, device development, and whole-organ manipulation are more