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2025 Volume 6, Issue 3
Cell Biology Research
ISSN: 2529-7627 (Online)

Research Progress of Tracheal Stent in Vitro and Animal Experiments

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Abstract: Tracheal stent implantation is a common method in clinical treatment of benign tracheal bronchial stenosis and tracheal bronchial fistula. With the widespread application of tracheal stent implantation, mucosal ulcer, tracheal restenosis, granulation and other complications of tracheal stent implantation are increasing, and relevant tracheal stent implantation in vitro and animal experiments are needed to test the effect of tracheal stent implantation. This paper summarized the status and development of in vitro testing and animal experimental research on tracheal stents in recent years, which laid the foundation for subsequent research and development of related technologies.

Keywords: Tracheal stent; Tracheal stenosis; Animal experiments; In vitro experiment

Online publication: September 26, 2025

1. Introduction

With the development of interventional radiology, especially the rapid development of high-resolution HRCT, the diagnosis rate of airway diseases has also been greatly improved, especially tracheal stenosis and tracheal fistula. In order to solve the above problems, the rapid rise of interventional radiology and new interventional medical devices has led to the emergence of materials, designs, and performance of tracheal stents. The implantation and removal technology of tracheal stents is constantly improving and has been widely adopted. This article summarizes the research status and latest progress of tracheal stents in vitro and animal experiments by analyzing the anatomical structure of the human airway and the basic differences in airway structure of commonly used experimental animal breeds, and organizing previous animal experimental research literature on tracheal stents. It provides a reference for subsequent research and development.

2. Anatomical analysis of the human trachea

2.1. Anatomy of the human main trachea

The main trachea of the human body is a circular tube that extends from the throat to the bronchi, with a relatively flat posterior wall[1]. The length of an adult's trachea is approximately 11 to 13 centimeters, which can be divided into two parts: the neck and chest. The cervical trachea descends along the midline of the neck, covering the sternohyoid muscle and sternocleidomastoid muscle in front, adjacent to the esophagus in the back, and accompanied by the inferior laryngeal nerve, blood vessels, and thyroid lobes on both sides. The anterior part of the thoracic trachea is adjacent to the aortic

arch and its branches (unnamed artery, left common carotid artery), unnamed vein, and thymus, while the posterior part is still close to the esophagus. In clinical routine tracheotomy, a midline incision is often chosen at the 3-4 or 4-5 tracheal cartilage rings[2]. The tracheal cartilage ring is C-shaped, and its posterior notch is connected by smooth muscle and elastic fiber tissue, forming a dynamic structure with certain elasticity to maintain airway patency and provide anatomical basis for biomechanical research of tracheal stents and other implanted instruments.

2.2. Anatomy of human bronchi

The bronchus is a primary branch of the trachea, including the left and right main bronchi. The left main bronchus is relatively slender, with an average length of about 4 centimeters, forming an angle of about 35-36 degrees with the central axis of the trachea. It runs relatively obliquely and enters the left lung through the left pulmonary hilum. The right main bronchus is relatively short and thick, with an average length of about 2-3 centimeters, forming an angle of about 22-25 degrees with the axis of the trachea. It runs relatively vertically and enters the right lung through the right pulmonary hilum. Due to the anatomical characteristics of the right main bronchus, foreign bodies in the trachea are more likely to fall into that side. This structural feature has important reference value in the construction of foreign body models involving tracheal stent implantation and animal experiments[3]. In addition, the bronchial branch structure and its epithelial cell types and functional differentiation provide key in vitro and in vivo experimental evidence for evaluating the cell biocompatibility and epithelial regeneration ability of tracheal stent materials.

3. Anatomy of related animal tracheas

3.1. Tracheal Anatomy of Rabbits

The trachea of rabbits is composed of 48-50 C-shaped cartilage rings, and the trachea below the cricoid cartilage narrows slightly after entering the chest cavity, and branches into the left and right main bronchi. The diameter of the right main bronchus is slightly larger than that of the left, and it branches into the upper lobe bronchus and enters the right lung apex lobe. The volume of rabbit lungs is relatively small, with the right lung being heavier than the left lung, weighing approximately 7-7.5 grams for the right lung and 5-5.5 grams for the left lung. The right lung is divided into 4 lobes, while there are different literature reports on the division of the left lung into 2 lobes or 3 lobes, mainly due to whether the left lung apex lobe is further divided into the anterior and posterior parts. The structure of rabbit tracheal cartilage and the composition of epithelial cells make it a commonly used in vivo model for evaluating the cell compatibility and epithelial regeneration ability of tracheal scaffolds.

3.2. Tracheal Anatomy of Small tailed Han Sheep

The trachea from the upper incisors to the glottis of the Small tailed Han sheep is about 18 centimeters long, and the subglottic trachea is about 30 centimeters long with a diameter of about 3 centimeters. The trachea is composed of a cylindrical long tube connected by a “C” - shaped cartilage ring and a cartilage membrane. It enters the chest cavity through the anterior opening and divides into left and right main bronchi at the level of the fifth thoracic vertebra, which enter the lungs. The right main bronchi also emit a small right apex lobe bronchus before branching off. The sheep trachea has a large size and stable cartilage ring structure, making it suitable for tracheal stent implantation surgery and medium - to long-term animal experimental studies on in vivo biocompatibility, epithelial differentiation, etc.

3.3. Tracheal Anatomy of Dogs

The tracheal structure of dogs includes the mucosal layer (pseudostratified columnar ciliated epithelium), submucosal layer, fibromuscular cartilage membrane, and outer membrane. The trachea starts from the throat, extends along the midline of the neck, enters the chest cavity through the anterior opening, and ultimately splits into the left and right main bronchi at approximately the 4th to 6th intercostal spaces. The right main bronchus is relatively short and thick, while the

left main bronchus is slightly slender. There are mucous glands and serous glands distributed within the tracheal mucosa, and the mucosal epithelium has dense cilia and secretory functions. The canine trachea is clearly divided into cervical and thoracic segments, with an anatomical structure similar to that of humans. The epithelial cell types and mucociliary clearance mechanisms are clear, making it a classic animal model for evaluating the biocompatibility of tracheal stent materials in vivo and their impact on respiratory epithelial cell differentiation[4,5].

4. Current research status of tracheal stents

4.1. Classification of new tracheal stents

Tracheal stents can be classified into three types based on their geometric shape: Y-shaped, T-shaped, and straight tube shaped. The “Y” - shaped stent is suitable for narrow or large fistulas in the tracheal prominence area, with stable fixation but complex release; The “T” - shaped stent can be used for subglottic stenosis, preserving vocal function but requiring an stoma; The straight tube stent is suitable for upper and middle tracheal lesions and is easy to insert but prone to migration. According to their structure, they can be divided into circular, mesh, and complex biomimetic types. Among them, 3D printed “C” ring scaffolds can better match the mechanical environment of tracheal cartilage, mesh covered scaffolds are used to seal fistula openings, and woven biomimetic scaffolds serve tissue regeneration.

From the perspective of materials science, tracheal stents are divided into two categories: non degradable and degradable. Non degradable stents such as metal, silicone, etc. provide long-lasting support but require secondary surgery to remove, which can easily cause inflammation and epithelial abnormalities. Degradable materials such as poly (p-cyclohexanone) (PDS), poly (lactic acid) (PLA), poly (caprolactone) (PCL), etc. not only have suitable mechanical properties and elastic recovery ability, but also have good biocompatibility and controllable degradation cycle, which can match the process of airway tissue healing, reduce long-term foreign body reactions, and support normal epithelial cell regeneration and functional differentiation. Therefore, they have attracted much attention in tissue engineering and regenerative medicine research.

4.2. Application of new tracheal stent

4.2.1. Tracheal stent for treating airway stenosis

Airway stenosis is divided into benign and malignant types, and in adults it is mostly acquired (such as iatrogenic, infectious, or foreign body). At present, metal or silicone stents are commonly used in clinical practice to treat malignant stenosis. For example, Xiong Zhen and other comprehensive methods such as high-frequency electrocautery, balloon dilation, and stent placement are used to treat benign central airway stenosis, and stents are selected according to the degree and location of stenosis, achieving good long-term efficacy[6]. However, long-term retention of non degradable materials can lead to impaired mucociliary clearance function, granulation hyperplasia, and abnormal epithelial cell differentiation. Therefore, current research focuses on biodegradable scaffolds, evaluating their effects on airway epithelial cell behavior, barrier function, and ciliary differentiation in vitro models and animal experiments, in order to promote physiological epithelial repair while maintaining mechanical support.

4.2.2. Tracheal stent for treating tracheoesophageal fistula

Tracheal esophageal fistula is often caused by congenital developmental abnormalities or acquired factors such as surgery, tumors, and infections. The treatment methods include surgery, stent placement, endoscopic techniques, and biological protein gel closure, among which tracheoesophageal stent placement has become mainstream due to its minimally invasive and efficient nature. Common types of stents include metal coated stents, silicone stents, 3D printed stents, and biodegradable stents. Straight stents are commonly used for the proximal trachea, while “L” or “Y” stents are suitable for the distal or protuberance regions. The outer diameter of the stent usually needs to be 10% -20% larger than the inner diameter of the trachea at the fistula site to achieve effective occlusion[7].

Studies at the cellular and animal levels have shown that the biocompatibility and surface properties of scaffold materials directly affect epithelial cell migration, differentiation, and fistula closure quality. For example, biodegradable materials such as PCL/PLA blend scaffolds have shown potential in in vivo experiments to promote mucosal regeneration, reduce leakage, and improve ciliary epithelial distribution. Although self expanding metal coated scaffolds have good adhesion and are easy to place, their long-term retention may still interfere with normal epithelial function. Therefore, a new type of biodegradable scaffold with a cell friendly interface has become a current research focus, aiming to achieve the dual goals of mechanical occlusion and tissue regeneration.

5. Current status of animal experimental research on tracheal stents

5.1. Preparation of animal models

In terms of animal model construction, domestic researchers have conducted multiple explorations. Li Zhaonan et al.[[8] selected New Zealand rabbits and studied the construction and performance of nano silver synergistic cisplatin eluting fiber scaffolds by inserting film coated and drug-eluting scaffolds. They found that it has potential in drug release and provides a reference for the functionalization of scaffold coatings. However, this study did not evaluate the scaffold effect under pathological conditions and further in vivo experimental verification is needed. Another study successfully established a rabbit model of tracheal stenosis by combining tracheotomy with nylon brush scraping of mucosa, and found that magnesium alloy stents were superior to nickel titanium alloy in terms of radial support and biocompatibility[9]. Zhao Chun et al.[5] used beagle dogs and constructed a model of tracheal stenosis under bronchoscopy guidance through electric burns and low-power disruption of mucosal continuity. This type of thermal and electrical injury method has the advantages of precise operation, good repeatability, and few complications. In addition, the canine trachea is similar in length and diameter to the human body, making it more suitable for simulating the in vivo biological reactions and epithelial repair process after stent implantation.

The commonly used methods for constructing animal models of tracheoesophageal fistula include azithromycin induction, surgical incision, and magnetic compression. The surgical incision method is easy to operate and widely used. For example, Yang Xinyue et al.[10] successfully established a tracheal fistula model through a midline incision in the neck of beagle dogs; Li Shuixiu et al.[11] used magnetic compression to construct a rabbit model of tracheoesophageal fistula. This non-invasive method has fewer complications and provides new ideas for fistula repair and re epithelialization research.

There is relatively little research abroad, and most of it focuses on models of tracheobronchial softening. Ha J et al.[12] implanted stents into healthy pigs and validated the compression mechanical model of the stent and its effectiveness in the treatment of tracheobronchial softening. They found that nickel titanium spiral stents significantly improved stenosis. Mondal et al.[13] established an in vitro softening model by excising sheep tracheal cricoid cartilage, providing a new method for optimizing the mechanical properties of scaffolds and connecting in vivo and in vitro models. Ruegemer JL et al.[14] used piglets to evaluate the effectiveness of balloon expandable metal stents in treating tracheal stenosis, indicating that the model is suitable for simulation studies on the treatment of tracheal stenosis in children.

Overall, domestic research often uses small animals such as rabbits and mice, which are low-cost and easy to operate; However, foreign countries tend to use large animals such as pigs, sheep, and dogs, whose airway structures are more similar to those of the human body, which is more conducive to simulating scaffold tissue interactions and epithelial differentiation processes at the physiological and cellular levels.

5.2. Current Status of Experimental Research

Currently, domestic research mainly focuses on material modification, drug release, and structural design of tracheal stents. Li Zhaonan et al.[7] developed an electrospun coated scaffold containing nano silver and cisplatin, which can significantly inhibit the growth of various pathogens and biofilm formation, demonstrating good antibacterial performance and cell

compatibility. Li Yahua et al.[15] developed arsenic trioxide eluting nanofiber scaffolds and confirmed in a rabbit model that they can promote tracheal epithelial regeneration and fistula repair. Zhao Chun[5] used electrospray technology to prepare paclitaxel eluting scaffolds, which effectively inhibited granulation tissue proliferation and restenosis, indicating the potential of drug sustained-release scaffolds in regulating local cell behavior and tissue repair.

In terms of stent structure, some scholars have explored the application of grass based composite materials and 3D printed concave hexagonal filling models in airway stents, and found that they have good mechanical adaptability and printing feasibility. Yuan Zhengchao et al.[16] developed a composite aerogel scaffold by combining 3D printing and electrospinning technology. The scaffold showed stable mechanical properties, good blood compatibility and biocompatibility in both in vitro and in vivo experiments, and was suitable for tracheal cartilage repair.

Foreign research also focuses on the biological response and restenosis mechanism of scaffold materials. Arellano Orden et al.[17] compared paclitaxel eluting stents, nickel titanium alloy, and cobalt based alloy stents in a rabbit model and found that early elevation of IL-8 in the blood after implantation can predict the progression of tracheal stenosis, providing a biomarker basis for evaluating the inflammatory response and epithelial abnormal differentiation caused by stents. Ruegemer JL et al.[14] placed balloon expandable metal stents in young pigs and avoided complications caused by excessive dilation by adjusting balloon parameters. Chaure J et al.[18] simulated the fluid dynamics interaction between the airway and vascular stent in rabbits and found differences in stress distribution among different metal materials.

It is worth noting that current research is increasingly introducing cellular biology evaluation indicators into animal models, such as epithelial barrier function, ciliary differentiation degree, inflammatory factor expression, and collagen deposition, in order to comprehensively evaluate the biocompatibility of tracheal stents and their impact on airway tissue regeneration in the in vivo environment.

6. Summary and outlook

With the continuous development and clinical application of new tracheal stents, stent implantation has become increasingly mature in the treatment of tracheal stenosis and tracheoesophageal fistula. However, postoperative complications such as stent displacement, mucus retention, restenosis, and epithelial repair still occur from time to time. The material characteristics, structural design, and surface coating of the stent not only affect its mechanical properties, but also directly regulate the behavior of host cells, such as epithelial cell proliferation and differentiation, inflammatory response, and ciliary function recovery, thereby determining long-term efficacy.

Future research needs to further combine in vitro cell models with animal experiments to systematically evaluate the biocompatibility of tracheal stents, especially biodegradable materials and biologically active coating stents. The focus should be on investigating the effects of scaffold materials on the differentiation and barrier function of airway epithelial cells, and verifying their effects on promoting tissue regeneration, inhibiting granulation tissue proliferation, and reducing fiber wrapping in an in vivo model. At the same time, it is necessary to optimize the selection of animal species and modeling methods to improve the clinical predictive value of experimental results.

Looking ahead to the future, developing new personalized tracheal stents with good cell compatibility and epithelial repair function based on different etiologies and lesion characteristics will be an important direction for achieving precise treatment and improving patients' long-term prognosis.

Disclosure statement

The author declares no conflict of interest.

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