Development of a novel tissue-engineered nitinol frame artificial trachea with native-like physical characteristics

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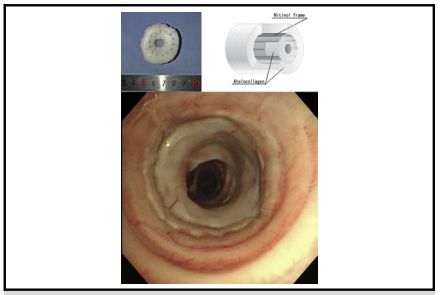
ABSTRACT

Background: Tracheal reconstruction is complicated by the short length to which a trachea can be resected. We previously developed a biocompatible polypropylene frame artificial trachea, but it lacked the strength and flexibility of the native trachea. In contrast, nitinol may provide these physical characteristics. We developed a novel nitinol frame artificial trachea and examined its biocompatibility and safety in canine models.

Methods: We constructed several nitinol frame prototypes and selected the frame that most closely reproduced the strength of the native canine trachea. This frame was used to create a collagen-coated artificial trachea that was implanted into 5 adult beagle dogs. The artificial trachea was first implanted into the pedicled omentum and placed in the abdomen. Three weeks later, the omentum-wrapped artificial trachea was moved into the thoracic cavity. The thoracic trachea was then partially resected and reconstructed using the artificial trachea. Follow-up bronchoscopic evaluation was performed, and the artificial trachea was histologically examined after the dogs were sacrificed.

Results: Stenosis at the anastomosis sites was not observed in any dog. Survival for 18 months or longer was confirmed in all dogs but 1, which died after 9 months due to reasons unrelated to the artificial trachea. Histological examination confirmed respiratory epithelial regeneration on the artificial trachea's luminal surface. Severe foreign body reaction was not detected around the nitinol frame.

Conclusions: The novel nitinol artificial trachea reproduced the physical characteristics of the native trachea. We have confirmed cell engraftment, good biocompatibility, and survival of 18 months or longer for this artificial trachea in canine models. (J Thorac Cardiovasc Surg 2018;156:1264-72)



A novel collagen-coated nitinol frame artificial trachea implanted in a canine model.

Central Message

This novel collagen-coated nitinol frame artificial trachea reproduced the physical properties of the native trachea. Good biocompatibility was confirmed in canine models.

Perspective

A collagen-coated nitinol frame was used to produce an artificial trachea with similar physical characteristics as the native trachea. This novel artificial trachea was implanted in dogs, where it demonstrated cell engraftment, good biocompatibility, and survival of 18 months or longer. These findings represent the first step toward the clinical application of this artificial trachea in human patients.

See Editorial Commentary page 1273.

See Editorial page 1263.

Tracheal reconstruction is sometimes indicated in the surgical management of various benign and malignant tumors. However, there is a limit to the length to which a trachea can be resected and reconstructed. Previous studies have reported that a 6-cm resection is the maximum length that allows subsequent anastomosis of the native trachea with current methods.[1,2] To overcome this limitation, the use of artificial tracheae has been extensively examined. Through in situ tissue engineering, we previously developed an artificial trachea in which a polypropylene mesh was molded

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Abbreviation and Acronym
CT = computed tomography

into a cylinder and coated with an atelocollagen layer.[3-9] Our experiments demonstrated that this collagen coating promotes regeneration of the autologous respiratory epithelium, which prevents exposure of the artificial trachea's luminal surface to external conditions.[3-9] This polypropylene frame artificial trachea demonstrated long-term safety and biocompatibility, and was successfully applied in a clinical setting[5]; however, it was unable to reproduce the strength, flexibility, and shape recovery properties of the native trachea for stabilizing the lumen against external forces.

To address these shortcomings, we focused on the use of nitinol as an alternative material for constructing artificial tracheae. Nitinol is a shape memory alloy that provides restoring forces against deformations resulting from external stress. Because of this characteristic, nitinol is used not only in industrial settings, but also in medical applications, such as the development of airway and vascular stents. A major advantage of using nitinol in stent production is that it enables the specification of material strength through changes in wire diameter and knitting patterns. We considered that this attribute may have similar applications in the development of artificial tracheae with physical properties that approximate those of the native trachea. Here we describe the development of a novel artificial trachea composed of a nitinol frame that reproduces the physical characteristics of the native trachea. The artificial trachea was coated with collagen using previously described techniques,[3-9] and we examined the biocompatibility and issues of this artificial trachea through implantation experiments in canine models.

METHODS

Development of the Artificial Trachea

Quantifying the mechanical properties of the native trachea. The native tracheal strength of adult beagle dogs was first measured to quantify the trachea's mechanical properties. Thoracic tracheae were collected from 5 dogs that had been sacrificed for another study. The mean length, width of the membranous portion, and distance from the ventral to the dorsal sides of the harvested tracheae were 80 mm, 22 mm, and 20 mm, respectively.

To measure the mechanical strength of the native trachea, each harvested trachea was placed between a force gauge (RZ-5; Aikoh Engineering, Osaka, Japan) and a cradle. The component of the force gauge that contacts the trachea measured $1.5 \times 5.0\ cm^2$, and the long axis of this component was placed perpendicular to the long axis of the trachea at the center of the cradle. The load applied to the force gauge was measured by raising the cradle, which moved from the posterior side of the trachea toward the anterior side (Figure 1, *A*). The load was measured 5 times for each sample, and these measurements were used to determine the strength required in the artificial trachea. The fitted curves of the mechanical strength measurements were generated using JMP 13 (SAS Institute, Cary, NC).

Constructing the nitinol frame. To construct the artificial tracheal frame, we used nitinol wire (0.18 mm diameter) composed of 55.9% nickel and 44.1% titanium (KIOKALLOY-R; Daido Steel, Nagoya, Japan). The shape recovery temperature of this alloy ranges between 20°C and 100°C, making it appropriate for in vivo use. The nitinol wire was molded into a continuous cylindrical shape using spool knitting. The cylindrical-shaped frame was heat-treated at 500°C for 15 minutes and then cooled with water (Marui Textile Machinery, Osaka, Japan). Two types of nitinol frames were initially fabricated: one with equal-width stitches (type A: 1.25-mm stitches) and another with unequal-width stitches (type B: 1.25-mm and 4.5-mm stitches) (Figure 1, *B*). The mechanical strength of both frames was quantified using the same method as for the native tracheae (Figure 2), and the type B frame was found to be stronger. However, the type B frame was still weaker than the native trachea. To more closely reproduce the native tracheal strength, another frame (type C; Figure 1, *B*) was developed with unequal stiches similar to type B but with smaller stitches in the major axis direction (0.75-mm). Because the type C frame had sufficient mechanical strength that was closest to that of the native trachea (Figure 2), this frame was chosen for use in the subsequent tracheal reconstruction experiments. The type C nitinol frame was shown to stabilize the lumen against elongation, twisting, and bending (Video 1).

Constructing the artificial trachea. We used a nitinol frame with a length of 30 mm and a diameter of 22 mm to construct each artificial trachea. The outer and inner surfaces of the nitinol frame were coated with 10 mm and 8 mm of 3% atelocollagen, respectively (Figure 3).[10,11] The collagen was frozen for 24 hours at −80°C and then freeze-dried under vacuum for 48 hours before undergoing thermal cross-linking for 12 hours at 140°C. The collagen was then sterilized before use.

Implanting the Artificial Trachea and Reconstructing the Trachea

The implantation surgery was performed in 5 adult beagle dogs in 2 stages (Figure 4). In the first surgery, laparotomy was performed under general anesthesia. A ventral midline incision of 5 cm was made, and the pedicled omentum was pulled to the outside of the abdominal cavity. The artificial trachea was wrapped in the omentum, which was then replaced into the abdominal cavity (Figure 4, *A* and *D*). This first surgery was aimed at preventing air leakage and infection of the artificial trachea through omentum wrapping.

The second surgery was performed 3 weeks after the first surgery using the same laparotomic approach. First, we confirmed that the artificial trachea was wrapped in the omentum. A hole was made in the right diaphragm, and the omentum-wrapped artificial trachea was guided from the abdominal cavity into the right thoracic cavity. Through the right thoracotomy, 20 mm of the thoracic trachea was resected (Figure 4, *B* and *E*) from the position where 3 to 4 cartilage rings remained from the tracheal bifurcation. Ventilation was provided via endotracheal tubes, and telescopic anastomosis was performed such that the native trachea was inserted 5 mm inside the artificial trachea. The segment bridged by the artificial trachea was 20 mm long (Figure 4, *C* and *F*). After checking for air leaks, the mediastinal pleura was sutured. The right lung was reexpanded through pressurization with a ventilator at chest closure, and the surgery was completed.

Evaluation

Follow-up observations were performed at 1, 3, 6, 9, 12, 18, and 24 months after the second surgery via bronchoscopy and computed tomography (CT) scans. The dogs were sacrificed at 18 and 24 months after the second surgery, and the artificial tracheae were resected with the surrounding tissues in en bloc fashion. After formalin fixation, the tissue blocks were cut along the longitudinal direction of the trachea such that the cut face of the nitinol frame was exposed. The excised tissues were embedded in paraffin, and the nitinol frame was removed from one side. Sections were prepared from the tissue surface on the opposite side from