Tracheal Transplantation
State of the Art and Key Role of Blood Supply in Its Success

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KEYWORDS

• Transplantation • Trachea • Immunosuppression • Cartilage • Revascularization

KEY POINTS

- Orthotopic tracheal transplantation is possible after heterotopic revascularization.
- Forearm provides a suitable and reliable revascularization site.
- Immunosuppressive drugs are necessary for tracheal allograft revascularization.
- Intercartilaginous incisions need to be made between every two cartilage rings and buccal mucosa grafts need to be introduced before immunosuppressive drugs can be safely withdrawn.
- Chondrocytes are immunologically privileged because they are protected within a matrix.

INTRODUCTION

Experience with tracheal allotransplantation has been anecdotal because of the difficulties linked with restoration of the blood supply. The first case of a tracheal allotransplant was reported in 1979.[1] Donor trachea was implanted heterotopically in the sternocleidomastoid muscle of the recipient and transferred to the orthotopic position 3 weeks later. However, the recipient was not given immunosuppressive therapy, no evidence of allograft viability was reported, and no information about the long-term outcome was published. The original article stated that "the tracheal allograft has become integrated and it has functioned perfect for 9 weeks without any evidence of rejection, ischemia, or infection."

A second case of tracheal allotransplantation was reported in 1993.[2] The allotransplant was revascularized orthotopically under protection of immunosuppressive drugs. The graft appeared vital at the end of the second month, but signs of graft stenosis appeared by the end of the fourth month. However, the transplant was not visualized in the paper. Current knowledge suggests that orthotopic revascularization of a tracheal graft is completely impossible (**Fig. 1**).

We began experimental animal research on tracheal allotransplantation in 1993.[3,4] In rabbits, the trachea was successfully transplanted in its orthotopic position after 2 weeks of heterotopical revascularization by wrapping in a vascularized fascia flap. From these studies, we learned that the trachea is subject to the same immunologic laws as all other allogeneic tissues. The most important component in tracheal rejection was lymphocyte-mediated, and the prime target cell population was the allograft endothelium.[4] In 2008 we attempted tracheal allotransplantation in the clinic.

LEARNING CURVE OF TRACHEAL ALLOTRANSPLANTATION

In 2008, we were confronted with a difficult clinical case of long-segment stenosis. Tracheal allotransplantation was considered as a possible

Disclosure: The authors have nothing to disclose.

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Thorac Surg Clin 28 (2018) 337–345
https://doi.org/10.1016/j.thorsurg.2018.05.002

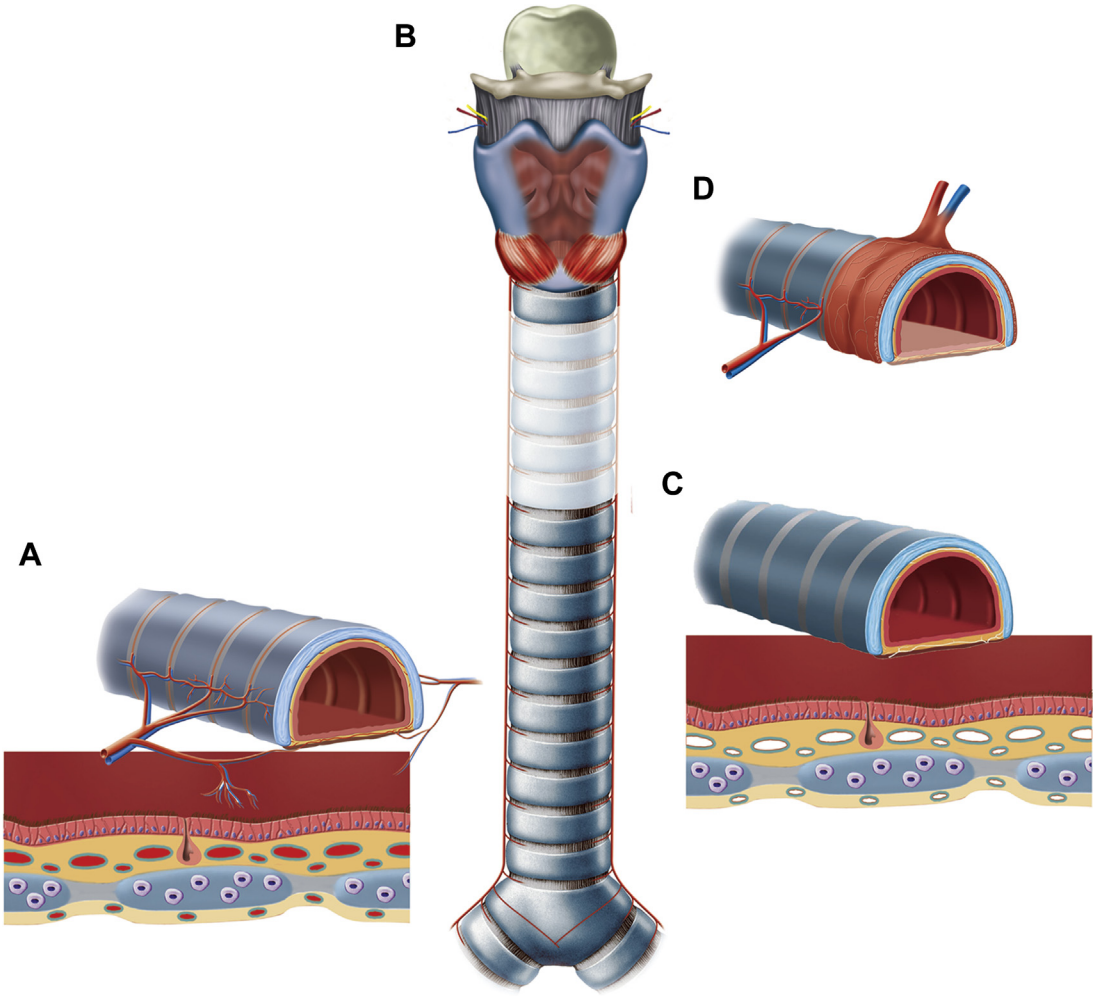

Fig. 1. Blood supply and tracheal transplantation. (*A*, *B*) Blood supply in the healthy native trachea is ensured by a network of small blood vessels that penetrate the trachea between the cartilage rings. (*C*) Prelevation of a tracheal segment inevitably leads to interruption of its blood supply. Successful transplantation requires restoration of an adequate blood supply (as in *B*), which is an extremely difficult process. (*D*) Devascularized tracheal segments can become revascularized in a heterotopic position. Direct orthotopic transplantation of the trachea is not possible regardless of whether the trachea is enwrapped with vascularized tissue. In humans, revascularization of the membranous trachea is difficult because the trachealis muscle forms a barrier for mucosal revascularization. Heterotopic tracheal revascularization safely occurs after excision of the membranous trachea (*D*).

solution for the patient's problem. Successful transplantation of a patch tracheal allograft was performed. The procedure involved the following key steps: (1) heterotopic revascularization of the cartilaginous trachea at the forearm under protection of immunosuppressive therapy; (2) replacement of the donor respiratory epithelium by recipient buccal mucosa; (3) withdrawal of immunosuppressive therapy; and (4) orthotopic transplantation, with anastomosis of the radial vascular pedicle to blood vessels of the neck. Withdrawal of immunosuppressive drugs was possible because of the immune-privileged status of chondrocytes within the cartilage rings. Because they are protected within a matrix, chondrocytes remain vital if they are perfused by diffusion through recipient blood vessels from surrounding tissues.[5,6]

Based on our experiences obtained in this first patient, we proposed the concept illustrated in Fig. 2 for subsequent patients.[7,8]

This concept was applied in six patients, including five patients with long-segment stenosis and one patient with a low-grade tracheal chondrosarcoma.[7,8] The patient with chondrosarcoma was a 63-year-old man whose tumor developed over a period of more than 10 years. His airway was preserved by placement of a silicone stent. Because of stagnation of secretions, he required