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EDITORIAL

Tracheal transplantation

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Non-malignant and malignant obstruction of the tracheal airway causes significant morbidity and mortality. With increased use of artificial airways, benign and iatrogenic complications are increasing. A tracheal stenosis < 5 cm in length can be resected with end-to-end anastomosis. Longer tracheal lesions can be treated in a palliative way by placement of a stent to secure airway lumen patency.

In recent years, most synthetic materials used for tracheal replacement have been tested in experimental animal research. From these studies, it is clear that airway repair is extremely difficult [1]. The reasons for the difficult repair of the airway tract are multifactorial. In contrast to vascular conduits, prosthetic replacement of the airway wall is not possible. First, the airway tract moves during respiration, swallowing, and coughing, and these movements interfere with the ingrowth of foreign material during healing. Most importantly, the internal site of the airway tract belongs to the outside world, and bacterial contamination at the interface between airway and prosthesis will prevent its ingrowth.

The management of tracheal defects is an evolving field. Tracheal transplantation and tracheal regeneration may bring major treatment advances to cases with long-segment tracheal involvement. This review examines the current possibilities in the area of tracheal transplantation.

Experience with tracheal allotransplantation has been anecdotal [2, 3] because of the difficulties linked with restoration of the blood supply. The segmental blood supply of the trachea originates from several tracheoesophageal branches that are too small to allow for microvascular transfer of tracheal segments [4]. Use of larger vessels will lead to invasive procedures without clinical application [5, 6]. Since the trachea lacks an identifiable vascular pedicle, the major challenge to successful tracheal transplantation is the safe restoration of the graft's blood supply [4]. Indirect revascularization of the trachea is possible, as evidenced by successful revascularization of a tracheal allograft after heterotopic wrapping in omentum [7] and successful transplantation of tracheal allografts and autografts involving vascularized fascial flaps in laboratory animals [8, 9] and humans [10–12]. This type of revascularization can be achieved by wrapping the tracheal allograft in heterotopic tissue from the recipient that is well vascularized and perfused by an identifiable vascular pedicle. Experiments in immunosuppressed rabbits showed complete revascularization and restoration of mucosal lining in tracheal allografts after 2–4 weeks of heterotopic revascularization in the lateral thoracic area [8]. 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 [8, 9].

On the basis of our experience with tracheal allotransplantation in animals and tracheal autotransplantation in patients, we decided to reconstruct a long-segment tracheal defect in a patient by using an allograft that was initially revascularized by heterotopic wrapping in vascularized fascia. Successful transplantation of a patch tracheal allograft was performed [13]. Based on our experiences obtained in this first patient, we proposed the concept illustrated in Fig. 1 for subsequent patients. 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) orthotopic transplantation, with anastomosis of the radial vascular pedicle to blood vessels of the neck; (4) withdrawal of immunosuppressive therapy. Withdrawal of immunosuppressive drugs was possible because of the immune-privileged

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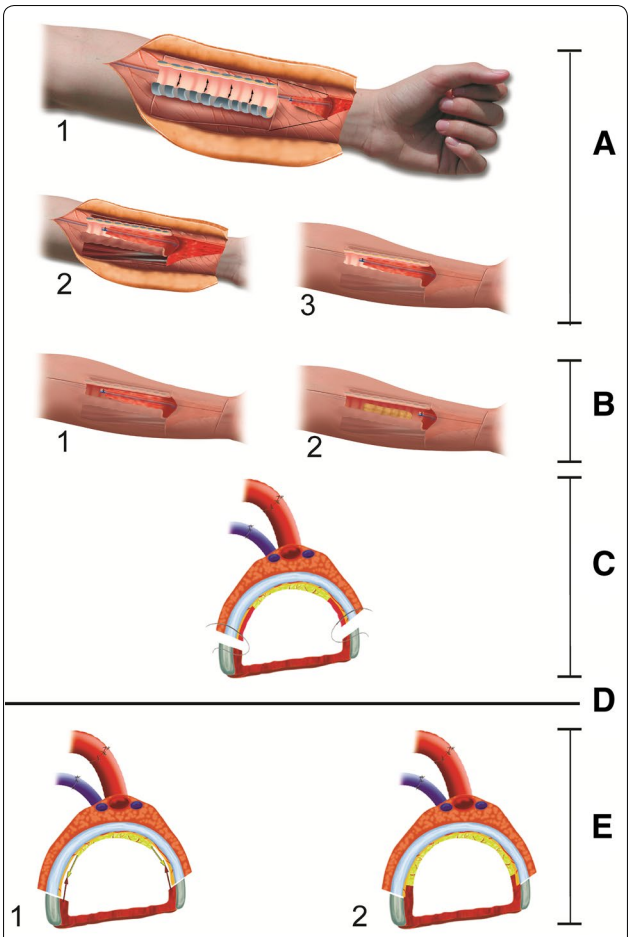

Fig. 1 Concept of tracheal allotransplantation. Concept of clinical procedure and timing of immunosuppression (Tacrolimus 9 mg/day, Cellcept 2 g/day, Medrol 24 mg/day). **a** Heterotopic allograft implantation. Freshly harvested tracheal allograft is wrapped with fascia and subcutaneous tissue on the radial side of the forearm. Before implantation, partial incisions (double arrows) are made in alternating anterior intercartilaginous spaces (1). Coverage of the luminal site of the transplant with well-vascularized tissue guarantees a fast mucosal revascularization and regeneration (2). Tracheal allotransplant after forearm implantation (3). **b** Heterotopic allograft revascularization. Revascularization allows the donor respiratory mucosa to regenerate, a process that is complete within 3 months (1). Once the graft is fully revascularized, the central portion of the respiratory donor mucosa is removed and replaced with a graft from the recipient's mouth mucosa (yellow). After ingrowth of the buccal mucosal graft, the inside rotated portion of the fascia flap is removed from the luminal site of the transplant (2). **c** Orthotopic vascularized transplantation. After ingrowth of the recipient mucosal graft, the revascularized tracheal graft can be transplanted orthotopically with its newly created vascular pedicle to repair the airway defect. **d** After orthotopic transplantation, immunosuppressive medication is gradually phased out and stopped. **e** Allorejection of donor noncartilaginous tissues. Withdrawal of immunosuppression provokes immunologic rejection of residual donor mucosal tissues (1). The donor cartilage is immune privileged and not susceptible to allorejection. Noncartilaginous tissues are replaced via outgrowth of the recipient buccal mucosa (yellow arrows) and recipient respiratory mucosa at the anastomotic sites (brown arrows) (1). (2) Replacement of noncartilaginous recipient-type tissues. Situation after healing of rejected donor mucosal lining

status of chondrocytes within the cartilage rings. As they are protected within a matrix, chondrocytes will remain vital if they are perfused by diffusion through recipient blood vessels from surrounding tissues [13, 14].

We learned that for safe withdrawal of immunosuppressants it was important to allow for growth of recipient blood vessels in the submucosal space of the graft. This growth could be guaranteed by making partial incisions through the intercartilaginous ligaments (Fig. 1). These incisions disrupted the barrier for angiogenetic outgrowth of recipient vessels and enabled ingrowth of recipient vessels into the submucosal space of the transplant [15].

Another important factor was the implantation of a recipient buccal mucosal graft in the central portion of the transplant (Fig. 1). Buccal mucosa was chosen because respiratory mucosa is difficult to handle as a free graft. After ceasing immunosuppressive therapy, all donor respiratory epithelium will disappear, and the buccal mucosal graft will progressively grow and recover part of the surrounding transplant's inner lining. The surviving recipient mucosal graft will allow for secondary healing of the necrotic areas of donor epithelial lining [16]. At transplant sites lined with nonciliated squamous epithelium, the loss of mucociliary clearance will be compensated through coughing.

With the intercartilaginous incisions and recipient buccal mucosa, immunosuppressive medication could be safely tapered and stopped 9–12 months after forearm implantation [15, 16]. Cartilage is avascular, relies on indirect nutrition from the surrounding tissues, and is well known to be immune privileged [14]. The revascularization procedure, along with carefully timed immunosuppression, takes advantage of these unique properties so as to preserve the tracheal cartilage tissue and structure, while noncartilaginous tissues are replaced by recipient tissues.

This concept was applied in six patients, including five with long-segment stenosis and one with a low-grade tracheal chondrosarcoma [13, 15]. The patients were intubated transorally to allow for insetting of the allograft into the tracheal defect. The endotracheal tube cuff was placed below the reconstructed airway segment, and cuff pressure was kept within the optimal range. Flap monitoring techniques included physical examination and handheld external Doppler sonography. The process of weaning and timing of extubation was started when the risk for flap failure was low. Extubation was possible in all six patients between 5 and 9 days after transplantation, and extubation failures were not encountered in our small series.

Our observations suggest that the trachea can be transplanted as a composite tissue with the cartilage structure

as the critical functional element of the graft. The technique holds promise for patients needing extensive airway reconstruction because the chimeric trachea graft does not require ongoing immunosuppression, a highly desired but elusive goal in the field of allotransplantation.

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