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The Role of Omentopexy in Tracheal Transplantation in Dogs

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The major step toward successful tracheal transplantation is revascularization of the grafted trachea. There are many reports that although omentopexy is an effective method to facilitate neo-vascularization in tracheal transplantations, the procedure has not been accepted universally in the transplantation field. It remains unclear whether an omentopexy can successfully revascularize tracheal graft regardless of the length of graft. This study was undertaken to assess the usefulness of omentopexy for long-segment(more than 4 cm) tracheal allotransplantation. We have performed six tracheal transplantations with omentopexy (group A) and four tracheal transplantations without omentopexy (group B) in mongrel dogs from July 1993 to February 1995. Five mid-portion tracheal rings were removed from ten donor dogs and ten corresponding tracheal rings were removed from the ten recipient dogs. The excised tracheal rings from the donors were transplanted to the recipient tracheal-excised sites. All the recipients were given cyclosporine, azathioprine, and prednisolone for immunosuppression in the post-operative period. The histologic results of all the surviving members of group B were better than those of the group A. These findings indicate that omentopexy has a limitation, it is not a major method for graft revascularization. Therefore the length of the tracheal graft was greater than 4.0 cm, for its viability, a longer tracheal graft requires some other blood supply aside from the omentopexy.

Key Words: Trachea transplantation, omentopexy

Extensive tracheal resection is often required in patients with malignant disease involving the trachea. It is also indicated in benign stenosis of the trachea resulting from accidental trauma or from congenital, inflammatory, or iatrogenic causes (Grillo *et al.* 1986). If a primary end-to-end anastomosis can not be performed to repair the extensive circumferential defect, conservative approaches such as laser therapy, stent insertion, or tracheostomy are often used. Therefore tracheal transplantation has been widely investigated although the results has been very poor.

In case of tracheal segments longer than 3.0 cm, it becomes very difficult to restore blood perfusion to the graft because of the small diameter of the tracheal vessels (Nakanish *et al.* 1993).

Experimental reconstruction of the trachea with autotransplants has been studied by several investigators and most experiments have been unsuccessful due to the difficulty in

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restoring blood circulation to the donor graft after anastomosis. There remains no blood supply to the donor graft other than the neovascularity that is passively derived from the recipient trachea during the course of wound healing (Alonso *et al.* 1972: Farrington *et al.* 1977). Neville *et al.* (1976a) reported that the tracheal lumen was patent when 3 tracheal rings were removed and then immediately reimplanted, but when 5 rings were implanted, dissolution of the cartilages and stenosis of the airways was noted. Although the blood supply from the recipient trachea is derived from both ends of the graft, an autograft longer than 5 rings can not maintain its structural integrity and there seems to be a limitation to the length of a tracheal autograft because revascularization of the graft can not be achieved. In the present studies, omentopexy was used as a facilitating method of revascularization for tracheal graft (Hirata *et al.* 1992).

This study was undertaken to evaluate the effect of omentopexy for tracheal allo-transplantation in dogs and the histologic findings were used to represent the grafts status.

MATERIALS AND METHODS

Animals and anesthesia

Ten adult mongrel dogs weighing 18 to 22 kg without gender discrimination were premedicated with an intravenous injection of entobar (30 mg/kg). They were placed in the supine position and intubated orally and connected to a pressure-limiting Harvard respirator (Harvard Apparatus Co.Inc.,S.Natick,Mass,USA). The dogs were kept under general anesthesia with halothane & intravenous injections of pentobarbital sodium (10 mg/kg).

All dogs received humane care in compliance with the "Principles of Laboratory Animal Care" reference formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institute of Health (NIH Publication No. 85-23, revised 1985).

Donor graft harvesting

Five rings of the cervical trachea were excised from all the ten donor dogs through an upper median sternotomy incision. The excised section of the tracheas was immersed in a cold University of Wisconsin(U.W) solution for one hour. The grafts were preserved at a cold temperature below 10℃.

Tracheal transplantation with omentopexy (Group A; n=6)

In the recipient dog, an upper midline laparatomy was made, and an omental pedicle fed by the right gastroepiploic artery was prepared and placed in the anterior mediastinum through the anterior diaphragmatic defect. A right anterolateral thoracotomy was made in the recipient dog. A total of ten tracheal rings were excised from the mid-portion of the recipient trachea, and a spiral endotracheal tube was inserted into the remaining lower trachea. At the same time the five tracheal rings were resected out from the donor trachea and stored in a cold University of Wisconsin solution for one hour. The allografts were then reimplanted with great caution in order to preserve the related blood supply. The anastomosis of the upper trachea and the lower trachea were similarly performed with running 4-0 Prolene sutures by telescope methods (Fig. 1). The endotracheal tube was pushed down further into the remaining lower trachea before the completion of lower anastomosis. At the same time, the spiral endotracheal tube was removed from the operative field.

The pedicle of the greater omentum was brought to the mid-portion of the transplanted trachea, and it was wrapped around both ends of the allograft. The thoracotomy and laparotomy incisions were then closed in the usual fashion, and the air in the pleural space was evacuated using the underwater seal drainage. The chest tube was removed before extubation.

Tracheal transplantation without omentopexy (Group B; n=4)

In this group, the omentopexy was not performed and therefore the only right anterolateral thoracotomy was made in all of the recipient

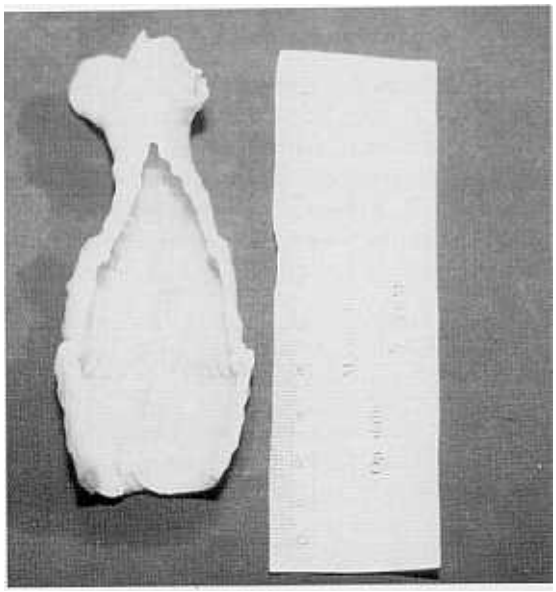

Fig. 1. *Gross feature of trachea anastomosis site with running 4-0 prolene sutures by telescope method.*

dogs. The ten tracheal rings were resected out from the mid-portion of the recipient trachea and five donor tracheal rings allografts were interposed as in the procedures of group A.

Postoperative management

All the recipients were given cephalosporine (1.0 gm/day, IV) and immunosuppressants such as cyclosporine (10 mg/kg, oral) and solumedrol (125 mg/day, IV) during the immediate post-operative course. The serum cyclosporine level was maintained at 300 μg/cc to 400 μ/cc with the weekly regular check up. Immediately after a dog died or was sacrificed, the transplanted trachea was excised for a histologic evaluation to determine the severity of the cartilage absorption and epithelial loss.

RESULTS

Of the six dogs in group A (with omentopexy), one died of pulmonary edema on the second post-operative day, another one, died of tracheal dehiscence on the third post-operative day, and four suffered from anorexia and general weakness, suggesting cyclosporine side effects (Table 1). One recipient died of tracheomalacia on the 44th post-operative day by rejection because the oral cyclosporin was skipped for 10 days due to the severe anorexia. Of the four dogs in group B (without omentopexy), one recipient died of pulmonary edema, one died of tracheal dehiscence; but the remaining two survived well (Table 2). In surviving members of group A (with omentopexy), the transplanted trachea revealed a moderate to severe infiltration of mononuclear cells in the subepithelium with marked fibrosis and absorption of the tracheal cartilage (Fig. 2). In surviving members of

Table 1. Tracheal transplantation with omentopexy (Group A)

Materials	Survival day	Cause of death
A−1		
A−2		
A−3		
A−4		
A−5		
A−6		

Table 2. Tracheal transplantation without omentopexy(Group B)

Materials	Survival day	Cause of death

Table 3. Histologic findings of grafts in the surviving members

Materials	Epithelial loss	Cause of death
A−4	server	severe
A−5	moderate	moderate
A−6	moderate	severe
B−3	abscent	abscent
B−4	abscent	abscent

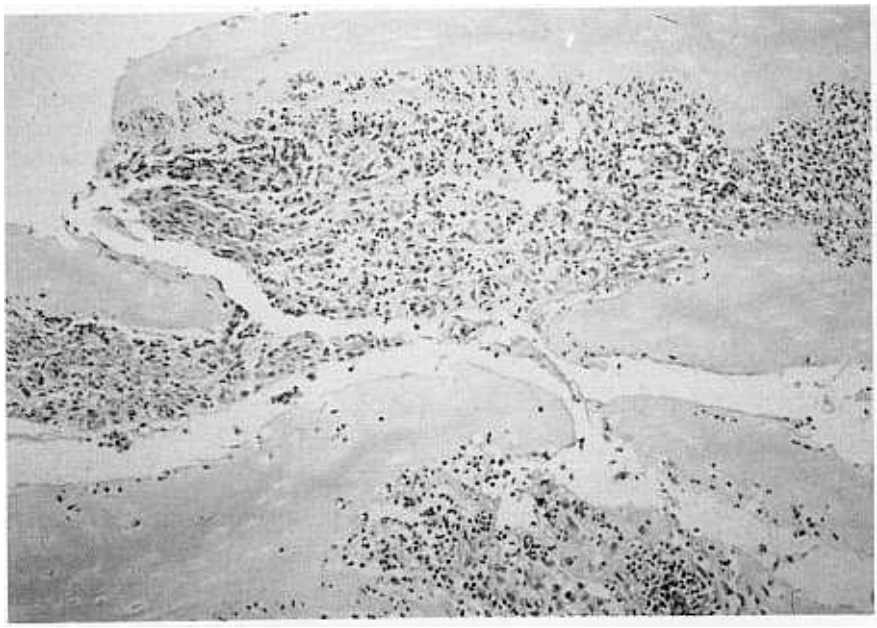

Fig. 2. Microscopic feature of transplanted trachea in group A showing the infiltration of the mononuclear cells in the subepithelium with marked fibrosis and absorption of tracheal cartilage.

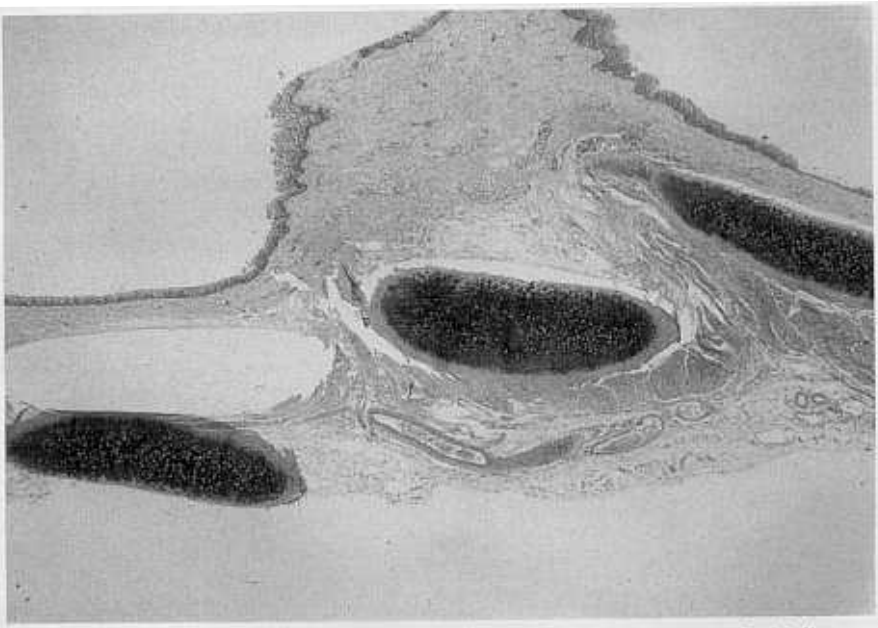

Fig. 3. Microscopic feature of transplanted trachea in group B showing the normal epithelium and cartilage.

group B, the surface of the grafts were covered with normal epithelium, and the tracheal cartilage was well preserved for three weeks after the transplantation when the animals were sacrificed (Fig. 3). Although we had a very short-term follow-up, these histologic findings in the surviving members showed that the post-operative results for group B were better than those for group A (Table 3).

DISCUSSION

An extensive tracheal resection is often required in patients with broad lesions involving the trachea or when a primary end-to-end anastomosis of the trachea is not feasible. In a study with cadavers, Mulliken and Grillo(1968) reported that the length of 4.5 cm of trachea could be resected and repaired by primary end-to-end anastomosis without undue tension. Grillo *et al.* (1964), reported that the length of the trachea for primary end-to-end anastomosis could be increased to 6.4 cm by full mobilization of the right hilum, division of the pulmonary ligament, and freeing the pulmonary vessels from the pericardium. However, these reports represented only technically feasible methods. The long term patency after extensive tracheal end-to-end anastomosis was unsatisfactory because almost all the cases failed to maintain the patency.

Tracheal reconstruction has been reported by numerous authors, and their efforts fall into three general categories: prosthetic replacement, autogenous tissue reconstruction, and homograft replacement (Grillo, 1990). The prosthetic graft replacement is beneficial to palliatively maintain the airway patency, but this method has many problems such as the ingrowing of granulation tissue, the chronic inflammation around the anastomosis site, the migration of the prosthesis; or the erosion of the major blood vessels (Shaha *et al.* 1988; Cull *et al.* 1990; Neville *et al.* 1990).

Grillo (1990) classified three general methods of autogenous tissue replacement among the various combinations. Those were cutaneous tube (Grillo *et al.* 1966), perichondrial tube (Krespi *et al.* 1983), and intestinal tubes using the esophagus (Kato *et al.* 1990) or the jejunum (Jones *et al.* 1986). The cutaneous tube and the perichondrial tube had many difficulties in clinical settings and were only used experimentally because of the complex techniques and few successes. The use of intestinal tubes such as the esophagus or the jejunum seems attractive because it reduces the anastomotic dehiscence and prosthetic migration, but the need for an artifical material to maintain the patency of the airway produces many discouraging problems (Kato *et al.* 1990).

In recent years, many studies regarding tracheal transplantation have been reported and these results should provide answers to solve many difficult problems. There are reports that effective immunosuppressive agents and irradiation will decrease the graft rejection (Inui *et al.* 1993) because the trachea is mainly composed of cartilaginous materials, and it shows a weak antibody response. Most investigators have concluded that graft rejection plays a minor role in the failure of graft and graft ischemia is the major cause for the graft failure (Balderman and Weinblatt, 1987).

The cervical trachea receives its blood supply primarily from the branches of the inferior thyroid artery, and the thoracic trachea receives blood from the innominate-subclavian system. Microscopically the tracheal blood vessels are intercartilaginous arteries derived from the lateral longitudinal anastomosis, and constructed as a rich vascular network beneath the endotracheal mucosa (Salassa *et al.* 1977). Once a tracheal graft has been separated from the donor trachea, it is difficult to restore blood perfusion to the graft because the tracheal vessels are very fine. A method of facilitating revascularization of the tracheal graft is therefore necessary.

Generally, the omentum has been utilized in a number of experimental models because of its angiogenic properties. The omentopexy has been shown to facilitate revascularization, and it has often been used to heal difficult sites such as bronchopleural fistula and bronchial anastomosis sites in lung transplantations. Lima *et al.* (1982), Morgan *et al.* (1993). Others have found that application of the highly vascular omentum to an avascular bronchial autograft 2 cm in length

resulted in early revascularization and prevented graft necrosis with its ensuing complications. Revascularization from omental blood vessels occurred within 4 days, and the epithelial loss and the tracheal necrosis, seen in control animals, was absent. Nakanish *et al.* (1994) reported that the pedicled flap of the greater omentum wrapped around the six-ring tracheal autograft was an effective method of neo-vascularization and graft survival. The inclusion of the gastroepiploic artery in the pedicle is an effective method for achieving an adequate blood supply to the vascularized omental flap (Messineo *et al.* 1991). The splenectomy allows for a sufficient length of pedicle to access all portion of the trachea (Moriyama *et al.* 1989). Another way of enhancing the omental revascularization of the trachea is by topical application of basic fibroblast growth factor, which accelerates the vascular ingrowth in a rabbit tracheal autotransplant model (Olech *et al.* 1991).

Among the various reports, it is still unclear whether the pedicled greater omentum wrapping can successfully revascularize a tracheal graft regardless of the length of the allograft. Neville *et al.* (1976b) reported that tracheal autografts longer than 4 cm demonstrated malacia of the mid-portion soon after the transplantation. Both a dye injection study and a laser estimation of the blood flow to the tracheal autografts suggested ischemia in their mid-portions. It was thought that the mid-portions of long autografts failed to receive the synergistic supplies from the native trachea and the omental pedicle.

In this study of the five tracheal ring graft, the graft survival was better for group B than for group A, which indicates that although the omentopexy is a method for facilitating revascularization of the tracheal graft but it is not a major method for graft revascularization.

In conclusion, it is possible to reconstruct an extensive tracheal defect by interposing a length-limited tracheal graft (less than 4.0 cm) under some tension. But the tracheal graft greater than 4.0 cm in length requires some blood supply other than the omental wrapping for its viability. Additional studies such as the synchronous revascularization of composite thyrotracheal transplantation (Khalil-Marzouk, 1993) and direct revascularization and venous drainage of tracheal graft (Paolo *et al.* 1994) were newly proposed experimental models to prevent or treat the ischemia following transplantation.

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