Accessory device fixation for voice rehabilitation in laryngectomised patients

Hallers, Egbert Jan Olivier ten

Chapter 5

Experimental results of the tracheo-esophageal tissue connector for improved fixation of shunt valves in laryngectomized patients

E.J.O. ten Hallers
H.A.M. Marres
E.B. van der Houwen
J.A. Jansen
G. Rakhorst
H.K. Schutte
T.G. van Kooten
J.-P. van Loon
G.J. Verkerke

Accepted for publication in Head and Neck 2006.

Abstract

Background

After total laryngectomy and voice rehabilitation using a tracheo-esophageal shunt valve, patients often suffer from valve-related complications such as leakage. To solve these problems, a tracheo-esophageal tissue connector (TE-TC) was devised to serve as an interface between the patient's tissue (trachea and esophagus) and the shunt valve.

Methods

The TE-TC is a permucosal connection constructed from a titanium ring (filled with a silicon rubber plug) combined with polypropylene (PP) or titanium mesh. After implantation in adult goats for 12 weeks the implants were submitted to histological investigation.

Results

Firm implant fixation was achieved. In nearly all (18/19), no signs of infection of the implant was seen. 11/19 animals died before the end of the experiment due to complications not related to the implant.

Conclusions

The TE-TC is a new device with potential in the solution for fixation-related problems in tracheo-esophageal voice rehabilitation.

1. Introduction

Voice rehabilitation in Western Europe and USA after laryngectomy is primarily initiated by means of a tracheo-esophageal (TE) shunt valve. Daily use of this valve is preferably combined with heat and moisture exchange (HME) filters and tracheostoma valves[1-3].

Concerning the shunt valve however, many laryngectomized patients suffer from valve-related complications such as leakage[4]. This results in coughing and in some cases in recurrent pneumonias. Frequent valve replacement has a negative influence on patients' quality of life. Two types of leakage can be distinguished. Leakage *through* the shunt valve and leakage *around* the shunt valve[4,5]. The first type of leakage is generated by valve dysfunction mainly caused by biofilm formation. This process and its solution has been and is still being studied extensively[6,7]. The second type of leakage is caused by incongruence between the size of the shunt valve and that of the fistula in the TE wall (peri-prosthetic leakage)[8]. This is the second most common reason for valve replacement[9] .

A small diameter of the TE fistula can be enlarged with a dilatator. For correction of an enlarged fistula, various options for treatment are available. Conservative treatment consists of temporary removal of the shunt valve resulting in the need for naso-gastric feeding. In most cases the fistula will shrink. A submucosal circular suture can also resolve leakage around the valve but this too does not contribute to a long-lasting solution. The same is true of repeated application of silver nitrate.

Many manufacturers have started to produce shunt valves with larger diameters resulting in a tighter fit. However, this probably also contributes to a higher frequency of leakage[10].

In a previous Eureka project[11] a concept of a *tracheo-esophageal tissue connector* (TE-TC) was developed[12,13]. A TC is thought to serve as an interface between the patient's tissue (trachea and esophagus) and the shunt valve itself. The main advantage is that it widens the choice of biofilm resistant materials for a valve system and/or voice producing elements (see figure 1).

The TE-TC is a permucosal connection and based on bone anchored percutaneous and permucosal connections such as the bone anchored hearing aid (BAHA)[14] pins for the fixation of maxillo-facial prosthetics[15], dental implants and soft tissue based implants[16-24] that were reported previously.

In the present Eureka project "Newvoice", the TE-TC concept was further developed into various prototypes. The aim of this paper is to determine the feasibility of the various prototypes by performing animal experiments and evaluating the histological reaction to the implant.

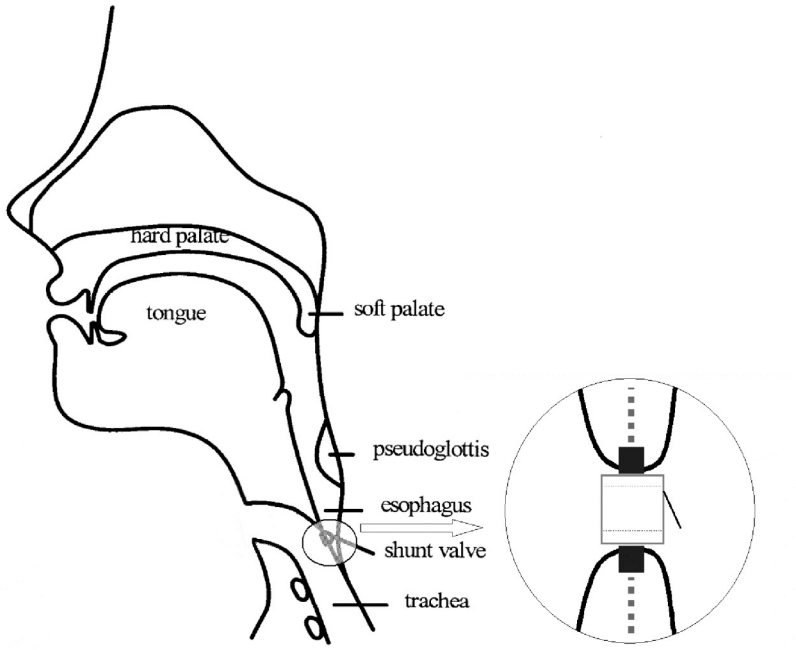

Figure 1. Schematical drawing of a laryngectomized patient with tracheo-esophageal tissue connector implanted.

2. Materials and Methods

2.1 Implants

Two prototypes of TE tissue connectors were tested. The first TE-TC consisted of a ring made of commercially pure titanium grade 2 (Thijssen Krupp B.V., Netherlands) and a polypropylene (PP) mesh (see figure 2a). The ring was designed to allow easy connection and disconnection of a shunt valve. The mesh itself was meant for capillary and fibrous tissue ingrowth to immobilize the implant resulting in a water and air tight connection device for valve systems.

The second TE-TC was provided with a more rigid titanium mesh instead of a PP mesh (figure 2b).

The rings were ultrasonically cleaned in a RBS soap solution, rinsed in water and cleaned in trichloroethylene and rinsed again in hot water and dried to the air. The surface characteristics (roughness and chemical composition) were comparable with the implants reported previously[25].

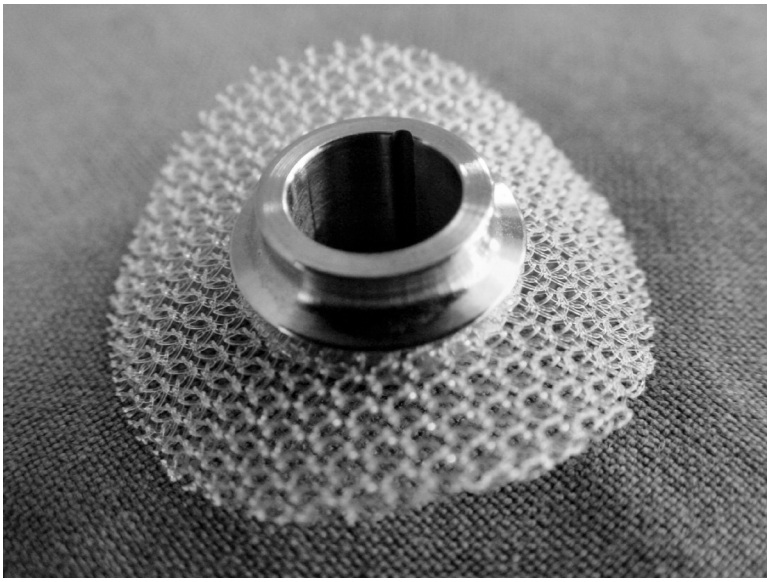

Figure 2a. Tracheo-esophageal tissue connector (TE-TC) with polypropylene mesh.

Figure 2b. Tracheo-esophageal tissue connector (TE-TC) with titanium mesh.

The knitted monofilament PP mesh (Bard® Mesh, Bard Benelux N.V., Netherlands) was cut to the appropriate size and cleaned in alcohol 70%. The titanium mesh consisted of 50 micron sintered fibers with a porosity of 80%, 500g/m^2 (N.V. Bekaert S.A., Belgium). The titanium mesh was cut into circular patches using a laser and argon gas. Afterwards it was cleaned in trichloroethylene and rinsed in boiling distilled water and dried. Both meshes had an outer diameter of 30mm. The meshes were glued to the titanium rings using MED-1511 RTV medical grade silicon adhesive (NuSil Technology, Carpinteria, USA) and a special Glue apparatus (I&J Finsar Inc.® JBE 1113, Eltest, Belgium) for controlled adhesive application. The implants were sterilized in an autoclave (121^{0}C for 20 minutes). Two different types of plugs for placement during implantation were made to fit in

the titanium ring. Plug-1 was designed to prevent debris and fluid collection in the lumen of the ring. Plug-2 was designed for the same function as plug-1 but also to guide the tracheal mucosal to the ring and enhance tissue attachment and connection to the titanium ring. Plug-2 contains two foldable flanges (comparable with an adapted shunt valve) with grooves in it, to ease folding. Both plugs were made of medical grade silicone rubber (MED-6033 silicone elastomer, (NuSil).

2.2 Surgical procedure

Adult female Saane goats (2.5-3 years, 60-80kg) were selected for this experiment because of the similarity in the dimension of the most relevant structures (trachea and esophagus)[26], they were easy to handle, the relevant structures were surgically relatively easily accessible and adequate numbers were available. The animals were individually housed according to national and institutional guidelines. The project was approved by the Ethical Committee for animal experiments of Radboud University Nijmegen Medical Centre. The implantation time was 12 weeks. Group 1 received the TE-TC with PP mesh. In group 2, instead of a TE-TC with PP mesh, titanium mesh was used. The surgical procedure was the same as for group 1. Also a pilot study was performed: in this pilot group 3, only the technical feasibility was tested. The initial surgical procedure of group 3 was identical to that of group 1 and 2. However, instead of silicone rubber plug-1, plug-2 was inserted after suturing the PP mesh to the trachea (using four vicryl 4-0 sutures) and puncturing the dorsal tracheal wall. The anterior flange of plug-2 was placed in the lumen of the trachea. For anesthesia the animals received medetomidine (Domitor®) (A.U.V., Cuijk, Netherlands) 25 µg/kg i.m., pentobarbital (Nembutal®) (A.U.V) 10-20 mg/kg i.v. and propofol 2mg/kg bolus and 8mg/kg/h maintenance i.m. Inhalation anesthesia was achieved by tracheal intubation and ventilation with O_2 (30%), N_20 (70%), isoflurane ca. 1,5 %.

The surgery was performed under full sterile conditions. The frontal neck area was shaved, washed and disinfected with poviodone solution followed by covering with sterile blankets.

After a vertical median incision the trachea and esophagus were locally separated. A laryngo-tracheal separation was performed 3 semi-rings below the cricoid. Also 3-6 semi-rings were excised. The laryngeal pouch was closed using a soft-tissue border. A similar surgical procedure was previously described by Prince and Nasser[27]. After the tissue connector had been inserted and glued to the surrounding tissue with a fibrin tissue glue Tissucol Duo (Baxter B.V., Hyland Immuno, Netherlands) the trachea was sutured to the skin and the wound was closed with 2-0 Vicryl®.

2.3 Post-operative management

After the operation lateral and antero-posterior X-rays were taken to check the positioning and alignment of the tissue connector. The animals were equipped with a shortened tracheostoma canula (silicone rubber Provox® Lary Tube™ (Atos Medical, Sweden) and Shiley tracheostomy tubes (with inner canula) (Mallinckrodt Inc., St. Louis, U.S.A.). The canulas were fixed to the neck by means of an elastic cord around the neck or by plastic rings sutured to the skin 5 cm inferior and 2-3 cm lateral from the stoma. The goats received anti-biotic prophylaxis and analgesics for 3 days and after day 3 on indication (respiratory and other infections). The goats received stoma care 3x/day and later 4x/day strictly every 6 hours after adaptation of the protocol.It consisted of canula and stoma cleaning and intra-tracheal instillations of 10cc saline to provoke a coughing reaction. In this way the trachea and bronchi were mechanically cleaned and extra moistened. To enhance easy clearance of mucus, a mucolytic agent, dissolved in water (0.25 mg/kg), was administered twice a day orally.

Additional air humidifiers were installed to realize a relative humidity of 60% or higher. Three times a week flexible endoscopy was performed. Detailed post-operative care is described separately.[28]

2.4 Histological processing and evaluation

The fixation of the implant was verified manually. They were then preserved in formaldehyde and after removal of hairs and excessive tissue, dehydrated in mounting alcohol solutions and impregnated with methylmethacrylate (MMA). After 8 weeks the samples in the MMA were polymerized. Then sections were cut by means of a microtome. Three regular sections at least were made for histological scoring. The sections were stained with methylene blue and basic fuchsin. The aspects specifically examined were: capsule quality, capsule thickness, interface quality, epithelial downgrowth (only group 3) and interstitial tissue quality (only at the location of the mesh).

3. Results

3.1 Animal Model

The average follow-up time and range of group 1, 2 and 3 were 57.9 (7-110), 38.33 (6-131) and 44.5 (39-50) days, respectively. The follow-up (and implantation) time of 84 days was exceeded in 3 cases due to logistic reasons (1), attempt to control a local infection (1) and pilot surgery experiments (1).

Not all animals were kept alive until the intended date of termination due to reaching human end points defined in the protocol or sudden death. In total 11/19 of the animals were lost before the and of the experiment as a consequence of factors not related to the implant. Nevertheless, histological results of these animals were obtained. Post-operatively, problems with the fixation of the tracheostoma canulas were encountered[28]. Many of the animals developed a deprived area at the cranial point of the tracheostoma despite all efforts to prevent tissue damage.

3.2 Macroscopic findings

During the operation some inter-individual differences were found concerning the size and shape of the trachea, similar to those described previously[26]. In some cases this appeared to give a non-ideal placement of the TE-TC. A small dorsal ridge of the trachea allows pivoting (in lateral direction). Nevertheless, on X-rays the positioning was satisfactory in all cases (see figure 3).

In the goats that were lost during follow-up, obductions revealed mucous plug obstruction, pneumonia, cardiac decompensation or lung edema/ exudate (n=11).Remarkably, no related clinical signs of disease were observed in the days before they died. No goats had to be terminated because of problems related to the TE-TC.

In all but one, no signs of local infections were seen. No implants showed defects and all implants inspected after an implantation time longer than a week were fixed well between the tissues. In the pilot group 3, plug-2 served well for guiding the tracheal tissue between the silicone rubber flange and the middle part of the ring with mesh (see figure 4). In one case the tracheal mucosa showed a tendency of partial overgrowing the flange of plug-2. The puncture site could easily be inspected with a light-source. In all 19 cases no signs of leakage of the laryngeal pouch were observed.

3.4 Light microscopy

Assessment of the histological sections revealed a comparatively uniform tissue response for all implants in group 1 (n=11). Group 2 consisted of a set of data with implantation time ranging from 6 days to 131 days (n=6). The titanium mesh of the implants of group 2 induced less fibrous tissue and inflammatory reaction compared to the implants of group 1. The density of fibres in the titanium mesh is much higher. Consequently, there is a much clearer interstitium that can be distinguished compared to the PP mesh. In all implants more flexion was seen of the PP mesh than of the titanium mesh.

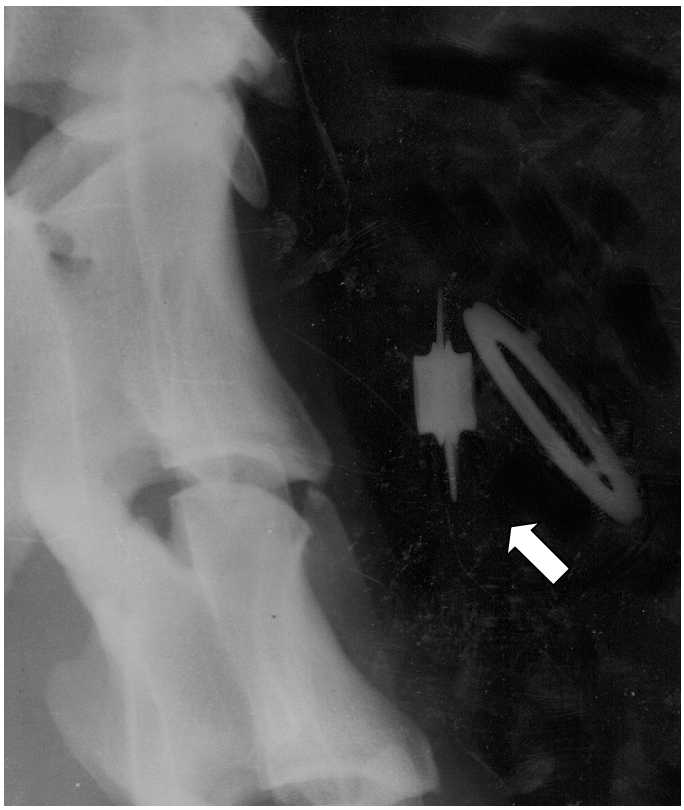

Figure 3. Lateral X-ray of the neck of a goat with tracheo-esophageal tissue connector (TE-TC) implanted with titanium mesh (white arrow) (Digitally enhanced).

Figure 4. Inferior view of cervical trachea just caudal from the implantation site. Note the intra-luminal tracheal flange of plug-2 and the abnormal dorsal tips of the cartilage semi-rings.

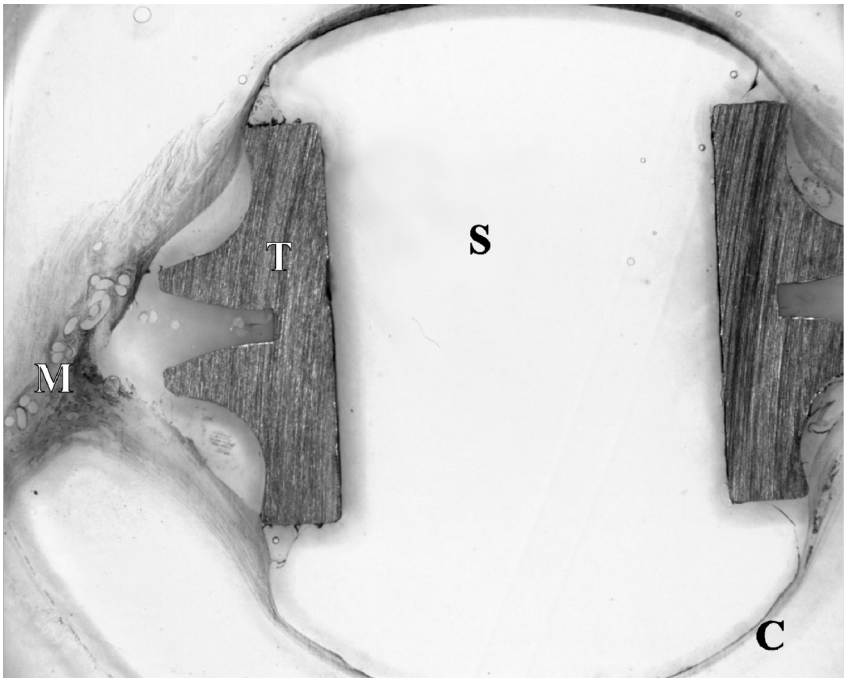

Figure 5. TE-TC with flexed polypropylene mesh after implantation of 12 weeks. Note the volume increase of the silicone rubber glue in the groove of the ring and plug-1. M: mesh fibres, T: Titanium ring, S: Plug-1, C: Fibrous capsule. 0.8x.

The fixation process induced a chemical reaction with the medical grade silicone rubber causing volume increase of the silicone rubber plugs (1 and 2) and the glue (used for fixation of the meshes to the ring). In most cases the sections showed a tissue interface that was not adjoining to the surface of the curvature of the titanium ring (see figure 5).

Implants of group 1 and 2 assessed after one week of implantation (n=2) showed many inflammatory cells (polymorphonuclear granulocytes and macrophages) and hardly any fibroblasts at the surface and the mesh. All samples showed many inflammatory cells close to the silicone glue and the fibrin tissue glue (see figure 6). After more than two weeks of implantation the tissues surrounding the implants showed increasing numbers of fibroblasts, increasing thickness of the fibrous capsule and a decrease in inflammatory cells.

Capsule quality improved in time of follow-up. After 12 weeks implantation time only a few inflammatory cells were present and the capsule density varied from dense around the titanium ring (see figure 7) to mature less dense around the mesh. Capsule thickness around the ring increased during follow-up. This varied from 5-20 layers at the mesh and the stop to 20-30 layers of fibroblasts around the ring.

After an implantation time of 7 weeks and beyond (n=7 of group 1 + 2), interstitial tissue of the mesh showed fibrous tissue with some blood vessels and only few macrophages.

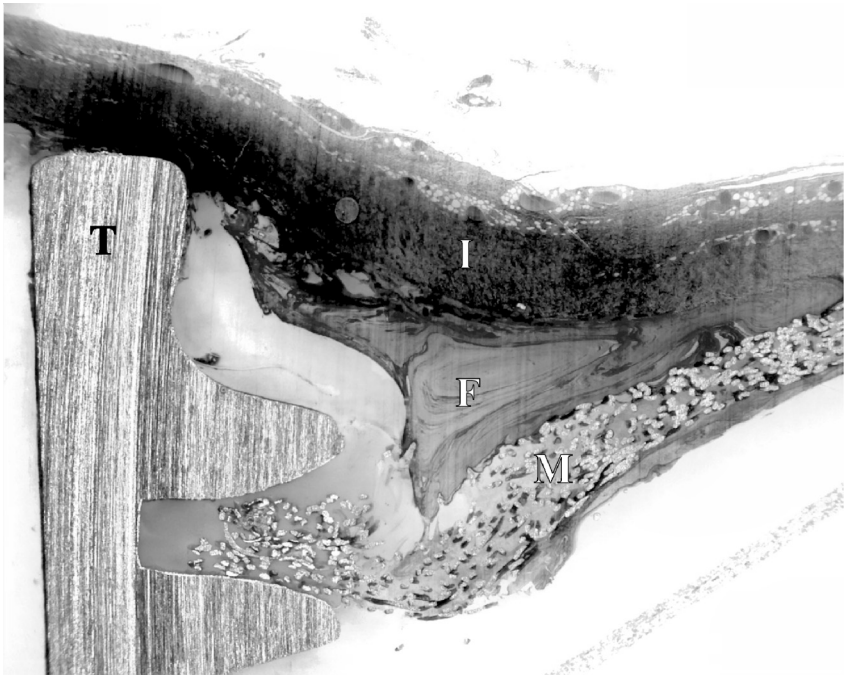

Figure 6. TE-TC with titanium mesh after implantation of 6 days. I: Inflammatory cells, T: Titanium ring, F: Fibrin tissue glue, M: Titanium mesh. (1.7x).

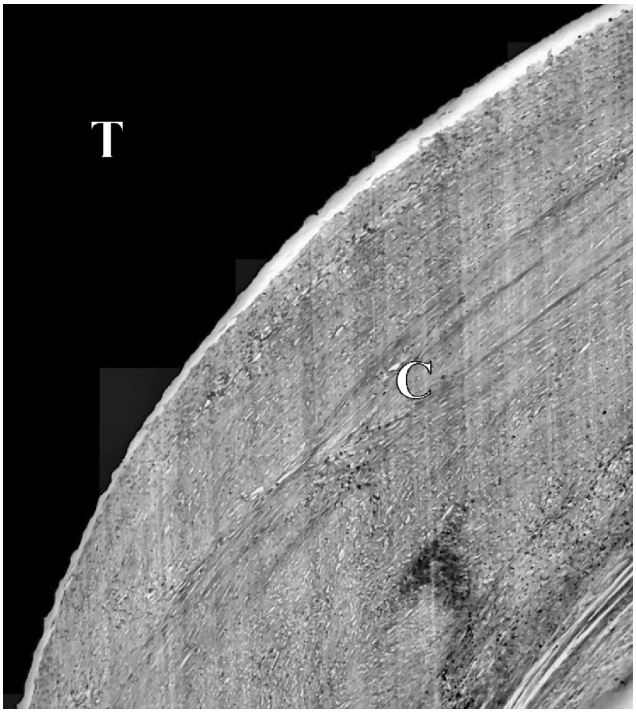

Figure 7. Close-up of the fibrous capsule (C) of curvature of the titanium ring (T) after implantation of 7 weeks and two days (group1). (10x).

The interface quality obtained at the site of the titanium ring and the silicone rubber plugs 1 and 2 evolved form multiple layers of macrophages until two weeks of implantation to fibroblasts contacting the implant surface without the presence, or only scattered foci, of macrophages or foreign-body giant cells. The implants of pilot group 3 (n=2) did not show signs of epithelial downgrowth along the plug-2 or titanium ring.

4. Discussion

Application of a TE shunt valve after total laryngectomy is the most successful component of voice rehabilitation. However, leakage both through the shunt valve and around this device requires life-long visits to an otolaryngologist to have the valve changed. Leakage around the valve is difficult to solve and has a detrimental effect on patients' quality of life.

The current solutions for resolving peri-prosthetic leakage e.g. injection of collagen solution, silicone macro particles such as a mixture of poly-dimethyl-siloxane (PDMS) and poly-vinyl-pyrrolidone (PVP) hydrogel (Bioplastique®, Bioplasty, Netherlands)[29,30], cross-linked hyaluronan (Hylaform®)[31], autologous fat[32,33], granulocyte-macrophage colony-stimulating factor (Molgramostim, GM-CSF), or application of sutures in the surrounding soft tissue[3,9] and the use of silver nitrate cautery for granulation tissue[34] illustrate that the ultimate solution has yet to be found. Surgical closure and a secondary puncture may be necessary in persistent cases. Worst case scenarios even include the need of reconstructions with an interposing pectoralis major flap (or other flaps) to close the fistula[34].

A tissue connector concept was developed to realize a complete leakage-free solution for TE speech. If the TE-TC also allows firm attachment and fibrous tissue ingrowth of the human esophagus, leakage around and through the shunt valve can be prevented and other materials can be used for the valve itself. The TE-TC may therefore contribute to enhancement of the quality of life of these patients.

Investigations in the past, aiming at improvements for laryngectomized patients and concentrating on developing an artificial larynx[11] and laryngeal transplantation[35,36], have not yet led to a sustainable or long-term solution. Therefore, development of shunt valves made of biofilm resistant material is currently at the focus of efforts to improve the quality of life for laryngectomized patients. This has resulted in a longer device life-time of the shunt valve[37].

When a TE-TC is implanted, the choice for materials for the valve itself is almost limitless. This means that materials less prone to biofilm adhesion are an option since the placement or replacement procedure does not require a flexible silicone rubber esophageal flange and there will no longer be any permanent interaction

with the tracheal or esophageal tissue. Concerning the TC itself, titanium and PP were materials chosen because of their biocompatibility[13,20,21,38]. Also Debry *et al.* pointed out that porous titanium would be the material of choice for constructs in the upper aerodigestive tract[39]. Macro-pores also contribute to a strong connection since they allow tissue bridges and prevent migration[40]. Tissue integration of PP mesh if infected is affected but the tensile strength does not change[41]. The medical grade silicone rubber glue was necessary for appropriate mesh fixation to the ring. However, this material provokes a relatively high foreign-body reaction and we prefer an alternative method of mesh fixation for the future.

Artefacts like gap formation between the soft tissue and the titanium ring may have been caused by mechanical forces during retrieval or fixation processing. In our samples, we suggest it was mainly caused by swelling of the silicone rubber[42], however this is not conclusive.

Continuous antibiotic treatment in goats with some kind of tracheostomy as proposed by Vogler et al.[43] was not appropriate here since this influences tissue reaction. There is no consensus whether continuous antibiotic treatment would improve the survival of goats with a tracheotomy or tracheostomy and additional veterinary research on this topic is desirable.

The tested TE-TC prototypes and plugs 1&2 were designed for a 2-stage implantation procedure since it may increase the chance of success[22]. The first stage consisted of implantation of a TC with plug-1 for 6 weeks. The intended second stage consisted of consequent punction of the dorsal tracheal wall, removal of plug-1, punction of the esophageal wall and installation of plug-2. However, esophageal puncture was not included: goats are ruminants, which increases the risk of complications and would not simulate the human situation. To test the TE-TC with an esophageal punction (or complete TE punction) in vivo, another non-ruminating animal model would be more appropriate. This, including tests in radiated tissue[44] will be tested in a future study. Because large-diameter TEPs involve the risk of leakage, titanium rings in particular should be kept as small as possible[10,45,46].

Soft tissue anchored implants have been reported to be successful in animal experiments although most of them deal with percutaneous connections instead of permucosal[13,22,38,47,48]. Knowledge about soft tissue embedded permucosal connections and implants is scarce[12] contrary to those in bone, such as dental implants[49.] Applications in humans, such as a titanium interface for a percutaneous transhepatic biliary drain[19] and connectors for body art and jewelry[24], illustrate that the soft tissue area around implants (the stress reduction area) can be controlled.

From the results of this study, it is concluded that a tracheo-esophageal tissue connector is a new device with potential in the solution of fixation-related problems in TE voice rehabilitation after laryngectomy. However, further research is needed to obtain long-term results of the tissue connectors when e.g. mechanically loaded with complete TE punction in a non-ruminating animal model.
The project will be finalized in the future by a first clinical application of the tissue connector with a voice-producing shunt valve.

Acknowledgements
We thank all co-workers and animal welfare officers of the Central Animal Facility, co-workers of the departments of BioMedical Engineering, Groningen, and Periodontology and Biomaterials, Nijmegen, the Netherlands. Also we express our gratitude to Mediprof-Atos Medical and Tefa Portanje for providing tracheostoma canulas.
This study was part of Eureka project 2614 “Newvoice” (http://www.eureka.be) and received financial support.

References

1. Verkerke GJ, Geertsema AA and Schutte HK (2002) Airflow resistance of heat and moisture exchange filters with and without a tracheostoma valve. *Ann Otol Rhinol Laryngol*, 111:333-337.
2. Hilgers FJM, Ackerstaff AH, van As CJ, Balm AJM, van den Brekel MWM and Tan IB (2003) Development and clinical assessment of a heat and moisture exchanger with a multi-magnet automatic tracheostoma valve (Provox FreeHands HME) for vocal and pulmonary rehabilitation after total laryngectomy. *Acta Oto-Laryngologica*, 123:91-99.
3. Op de Coul BMR, Hilgers FJ, Balm AJ, Tan IB, van den Hoogen FJ and van Tinteren H (2000) A decade of postlaryngectomy vocal rehabilitation in 318 patients: a single Institution's experience with consistent application of provox indwelling voice prostheses. *Arch Otolaryngol Head Neck Surg*, 126:1320-1328.
4. ten Hallers EJO, Marres HAM, Rakhorst G, et al. (2005) Difficulties in the fixation of prostheses for voice rehabilitation after laryngectomy. *Acta Otolaryngol,* 125:804-813.
5. Bunting GW (2004) Voice following laryngeal cancer surgery: troubleshooting common problems after tracheoesophageal voice restoration. Otolaryngol Clin North Am, 37:597-612.
6. Oosterhof JJ, van der Mei HC, Busscher HJ, et al. (2005) In vitro leakage susceptibility of tracheoesophageal shunt prostheses in the absence and presence of a biofilm. *J Biomed Mater Res B Appl Biomater*, 73:23-28.
7. Schwandt LQ, van Weissenbruch R, van der Mei HC, Busscher HJ and Albers FW (2005) Effect of dairy products on the lifetime of Provox2 voice prostheses in vitro and in vivo. *Head Neck*, 27:471-477.
8. Laccourreye O, Menard M, Crevier-Buchman L, Couloigner V and Brasnu D (1997) In situ lifetime, causes for replacement and complications of the Provox voice prosthesis. *Laryngoscope*, 107:527-530.
9. Brown DH, Hilgers FJ, Irish JC and Balm AJ (2003) Postlaryngectomy voice rehabilitation: state of the art at the millennium. *World J Surg*, 27:824-831.
10. Blom ED (2003) Some comments on the escalation of tracheoesophageal voice prosthesis dimensions. *Arch Otolaryngol Head Neck Surg*, 129:500-502.

11. Verkerke GJ, de Vries MP, Geertsema AA, Schutte HK, Busscher HJ and Herrmann IF (1997) Eureka project 'totally implantable artificial larynx'; progress report. In: McCafferty G, Coman W, Carroll R, editors. XVI World congress of Otorhinolaryngology Head and Neck Surgery. Bologna: Monduzzi Editore; p 1343-1346.
12. Geertsema AA, Schutte HK, Rakhorst G, van Luyn MJ, Mahieu HF and Verkerke GJ (2001) A novel tracheal tissue connector for fixation of laryngeal prostheses. *Biomaterials*, 22:1571-1578.
13. Geertsema AA, Schutte HK, van Leeuwen MB, et al. (1999) Biocompatibility of a novel tissue connector for fixation of tracheostoma valves and shunt valves. *Biomaterials*, 20:1997-2005.
14. Van der Pouw CTM (1999) Bone Anchored Hearing, short and long term results. Thesis. Radboud University Nijmegen.
15. Schoen PJ, Raghoebar GM, van Oort RP, et al. (2001) Treatment outcome of bone-anchored craniofacial prostheses after tumor surgery. *Cancer*, 92:3045-3050.
16. Grosse-Siestrup C and Affeld K (1984) Design criteria for percutaneous devices. *J Biomed Mater Res,* 18:357-382.
17. Jansen JA, van der Waerden JP and de Groot K (1991) Development of a new percutaneous access device for implantation in soft tissues. *J Biomed Mater Res*, 25:1535-1545.
18. Lundgren D and Axelsson R (1989) Soft-tissue-anchored percutaneous device for long-term intracorporeal access. *J Invest Surg*, 2:17-27.
19. Nyman R, Eklof H, Eriksson LG, et al. (2005) Soft-tissue-anchored transcutaneous port for long-term percutaneous transhepatic biliary drainage. *Cardiovasc Intervent Radiol*, 28:53-59.
20. Paquay YC, de Ruijter JE, van der Waerden JP and Jansen JA (1994) Titanium fiber mesh anchorage for percutaneous devices applicable for peritoneal dialysis. *J Biomed Mater Res*, 28:1321-1328.
21. Paquay YC, de Ruijter JE, van der Waerden JP and Jansen JA (1996) Tissue reaction to Dacron velour and titanium fibre mesh used for anchorage of percutaneous devices. *Biomaterials*, 17:1251-1256.
22. Paquay YC, de Ruijter AE, van der Waerden JP and Jansen JA (1996) A one stage versus two stage surgical technique. Tissue reaction to a percutaneous device provided with titanium fiber mesh applicable for peritoneal dialysis. *ASAIO J*, 42:961-967.
23. Walboomers XF, Paquay YC and Jansen JA (2001) A new titanium fiber mesh-cuffed peritoneal dialysis catheter: evaluation and comparison with a Dacron-cuffed tenckhoff catheter in goats. *Perit Dial Int*, 21:254-262.
24. Williams AM and Southern SJ (2005) Body piercing: to what depths? An unusual case and review of associated problems. *Plast Reconstr Surg,* 115:50e-54e.
25. Ten Hallers EJO, van der Houwen EB, Marres HAM, et al. (2006) Histological assessment of tracheostoma tissue connector prototypes. *Accepted J Biomed Mater Res Part A*.
26. Ten Hallers EJO, Rakhorst G, Marres HAM, et al. (2004) Animal models for tracheal research. *Biomaterials*, 25:1533-1543.
27. Prince ME, Nasser JG and Pass BB (1997) Effect of upper-airway passages on craniofacial growth in an animal model: a pilot study. *J Otolaryngol*, 26:306-315.
28. Ten Hallers EJO, Marres HAM, Rakhorst G, et al. (2005) The goat as animal model for post-laryngectomy research: practical implications. submitted.
29. Rokade AV, Mathews J and Reddy KT (2003) Tissue augmentation using Bioplastique((R)) as a treatment of leakage around a Provox((R)) 2 voice prosthesis. *J Laryngol Otol* 117:80-82.
30. Lichtenberger G (2001) Advances and refinements in surgical voice rehabilitation after laryngectomy. *Eur Arch Otorhinolaryngol*, 258:281-284.
31. Luff DA, Izzat S and Farrington WT (1999) Viscoaugmentation as a treatment for leakage around the Provox 2 voice rehabilitation system. *J Laryngol Otol*, 113:847-848.
32. Laccourreye O, Papon JF, Brasnu D and Hans S (2002) Autogenous fat injection for the incontinent tracheoesophageal puncture site. *Laryngoscope*, 112:1512-1514.
33. Perie S, Ming X, Dewolf E and St Guily JL (2002) Autologous fat injection to treat leakage around tracheoesophageal puncture. *Am J Otolaryngol*, 23:345-350.
34. Ferrer-Ramirez MJ, Guallart-Domenech F, Brotons-Durban S, Carrasco-Llatas M, Estelles-Ferriol E and Lopez-Martinez R (2001) Surgical voice restoration after total laryngectomy: long-term results. *Eur Arch Otorhinolaryngo*l, 258:463-466.
35. Akst LM, Siemionow M, Dan O, Izycki D and Strome M (2003) Induction of tolerance in a rat model of laryngeal transplantation. *Transplantation*, 76:1763-1766.

36. Strome M, Stein J, Esclamado R, et al. (2001) Laryngeal transplantation and 40-month follow-up. *N Engl J Med*, 344:1676-1679.
37. Hilgers FJM, Ackerstaff AH, Balm AJM, van den Brekel MWM, Tan IB and Persson J-O (2003) A new problem-solving indwelling voice prosthesis, eliminating the need for frequent candida- and "underpressure"-related replacements: Provox ActiValve. *Acta Otolaryngol*, 123:972-979.
38. Jansen JA, Paquay YG and van der Waerden JP (1994) Tissue reaction to soft-tissue anchored percutaneous implants in rabbits. *J Biomed Mater Res*, 28:1047-1054.
39. Debry C, Charles X, Frenot M and Gentine A (2000) Intra-laryngeal endoprosthesis: an alternative therapeutic approach to surgical procedures of laryngeal exclusion. *J Laryngol Otol,* 114:760-764.
40. Bessette RW, Cowper T, Natiella J, Meenaghan M, Shatkin S and Schaaf N (1981) Histological evaluation of pore size and shape in silicone implants in rhesus monkeys. *Ann Plast Surg*, 7:447-452.
41. Bellon JM, Garcia Carranza A, Garcia Honduvilla N, Carrera San Martin A and Bujan J (2004) Tissue integration and biomechanical behaviour of contaminated experimental polypropylene and expanded polytetrafluoroethylene implants. *Br J Surg*, 91:489-494.
42. Walboomers XF and Jansen JA (2005) Effect of microtextured surfaces on the performance of percutaneous devices. *J Biomed Mater Res A*.
43. Vogler GA, Keiichi Y, Frank PA and Baudendistel LJ (1992) Permanent tracheostomy in goats. *AALAS Bull*, 31:15-17.
44. Chone CT, Gripp FM, Spina AL and Crespo AN (2005) Primary versus secondary tracheo-oesophageal puncture for speech rehabilitation in total laryngectomy: long-term results with indwelling voice prosthesis. *Otolaryngol Head Neck Surg*, 133:89-93.
45. Eerenstein SE, Grolman W and Schouwenburg PF (2002) Downsizing of voice prosthesis diameter in patients with laryngectomy: an in vitro study. *Arch Otolaryngol Head Neck Surg,* 128:838-841.
46. Stafford FW (2003) Current indications and complications of tracheoesophageal puncture for voice restoration after laryngectomy. *Curr Opin Otolaryngol Head Neck Surg*, 11:89-95.
47. Gerritsen M, Paquay YG and Jansen JA (1998) Evaluation of the tissue reaction to a percutaneous access device using titanium fibre mesh anchorage in goats. *J Mater Sci Mater Med,* 9:523-528.
48. Jansen JA and van 't Hof MA (1994) Histological assessment of sintered metal-fibre-web materials. *J Biomater Appl,* 9:30-54.
49. Abrahamsson I, Zitzmann NU, Berglundh T, Linder E, Wennerberg Aand Lindhe J (2002) The mucosal attachment to titanium implants with different surface characteristics: an experimental study in dogs. *J Clin Periodontol,* 29:448-455.