

Kerstin Schümann*, Tamara Wilfling, Gerrit Paasche, Robert Schuon, Carsten Tautorat, Klaus-Peter Schmitz, Thomas Lenarz, Niels Grabow

Polymeric stents for the Eustachian tube: development and human cadaver study

Abstract: Impairment of Eustachian tube function with non-sufficient ventilation of the middle ear is a main cause for chronic otitis media. To provide an effective and safe therapy, the innovative concept of Eustachian tube stenting was established. Biodegradable polymeric stents are developed to restore impaired tube function and dissolve after fulfilling their supportive purpose.

To evaluate the applicability of the stents in the Eustachian tube, prototypes in conjunction with corresponding implantation instruments were tested in human cadaver studies. Radiopaque markers and a diaphanoscopy approach were tested as additional features to prove correct positioning of catheter and stent in the tube. In the current study biodegradable polymeric stents were implanted in the Eustachian tube of human cadavers without difficulty. Correct positioning of the stents in the tube was proved by diaphanoscopy during intervention and postoperative tomographic and histological analyses. Once designs are optimized on the basis of cadaver studies, preclinical safety and efficacy studies using animal models will be initiated.

Keywords: Eustachian tube dysfunction, polymeric stent, cadaver study, radiopaque marker, diaphanoscopy.

<https://doi.org/10.1515/cdbme-2020-3054>

***Corresponding author: Kerstin Schümann:** Institute for Biomedical Engineering, Rostock University Medical Center, Friedrich-Barnewitz-Str. 4, 18119 Rostock, Germany, e-mail: kerstin.schuemann@uni-rostock.de

Tamara Wilfling, Gerrit Paasche, Robert Schuon, Thomas Lenarz: Department of Otorhinolaryngology, Hannover Medical School, Carl-Neuberg Str. 1, 30625 Hannover, Germany

Carsten Tautorat, Niels Grabow: Institute for Biomedical Engineering, Rostock University Medical Center, Friedrich-Barnewitz-Str. 4, 18119 Rostock, Germany

Klaus-Peter Schmitz: Institute for ImplantTechnology and Biomaterials, Institute for Biomedical Engineering, Rostock University Medical Center, Friedrich-Barnewitz-Str. 4, 18119 Rostock, Germany

1 Introduction

Eustachian tube dysfunction (ETD) with non-sufficient ventilation of the middle ear may, among other things, lead to chronic otitis media. Prevalence of chronic ETD is about 1 % of adult population and is the main cause of permanent conductive hearing loss [1, 2]. Stenting of the Eustachian tube as treatment option is an innovative concept to restore impaired tube function.

Besides development and testing of permanent stents, we pursue concepts of biodegradable stents. Assuming the supporting effect of Eustachian tube stents is required only temporarily, the stents dissolve afterwards leaving no foreign body behind. Following cardiovascular stent technologies poly(L-lactide) (PLLA) or PLLA-based blends are considered as materials for biodegradable Eustachian tube stents.

Previous studies of our research team confirmed basic feasibility of Eustachian tube stenting in sheep as animal model [3]. On this basis, adapted stent designs as well as methods and tools for implantation were developed and pre-tested in several application studies.

In the current examination polymeric stents were implanted in the Eustachian tube of human cadavers using cardiovascular balloon catheters to prove structural access and feasibility of stent implantation. Besides, the capability of two approaches for optical and tomographic position control was analysed: (i) confirmation of the balloon catheter to be properly advanced to the Eustachian tube by diaphanoscopy and (ii) X-ray visibility of the implanted stent by means of integrated radiopaque markers.

2 Materials and methods

2.1 Fabrication of stent prototypes

To evaluate the applicability of biodegradable polymeric stents in the Eustachian tube, prototypes made of PLLA were

tested in human cadaver studies. The stent prototypes were fabricated from solution cast mini-tubes (inner diameter: 1.4 mm, wall thickness: 150 μm), according to [4], in a laser cutting process using a femtosecond laser. To enable enhanced mechanical stent properties, such as small elastic recoil and smooth expandability, stents were subjected to a thermo-mechanical treatment (expansion at 80 $^{\circ}\text{C}$, crimping at 50 $^{\circ}\text{C}$), according to [5]. With the crimping process the stents were mounted on standard coronary balloon catheters (BIOTRONIK Pantera Pro 3.5x15 mm).

2.2 Radiopacity

X-ray tomographic methods, esp. cone beam computer tomography (CT), are used to intra- or postoperatively control exact positioning of the stent in the tube. As the polymeric stent material is not X-ray visible, radiopaque markers [6] were incorporated in the stents. The stent design was adapted by generating two areas with appropriate dimensions (**Figure 1**). The markers are arranged with a 60 $^{\circ}$ shift around the circumference to ensure large-area visibility of at least one marker.

The markers were integrated in the stent prototypes by heat input in the upper marker surface using a soldering iron with a small copper bit (see **Figure 2**). To secure adherence of the marker, the stent is coated with PLLA using an airbrush spray coating procedure. Due to the intended application in cadaver studies there is no drug incorporated in the coating. However, a drug-eluting coating is planned for prospective preclinical or clinical studies.

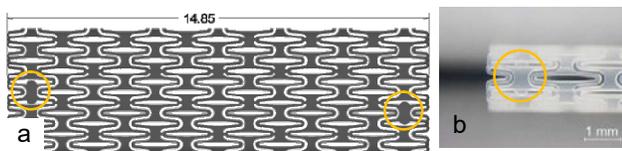


Figure 1: a) Unwind of the stent design and b) laser-cut stent with designated areas (yellow circle) for marker integration

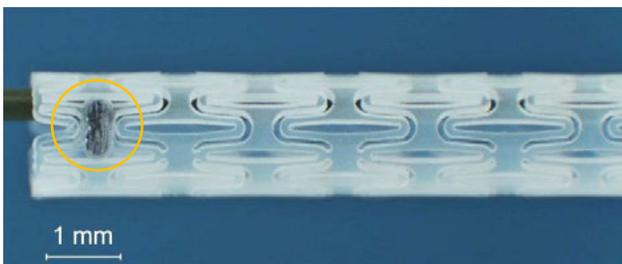


Figure 2: Polymeric Eustachian tube stent with integrated radiopaque marker

2.3 Diaphanoscopy

A potential complication of balloon catheter insertion is a *via falsa* (extratubular malposition in conjunction with tissue penetration). To prove correct positioning of the catheter in the Eustachian tube an experimental tool for diaphanoscopy was developed and tested. An optical fiber (diameter 0.25 mm), that was cut to the length required, was connected to a battery-operated red visible red LED emitter (see **Figure 3**). By advancing the optical fiber through the guide wire lumen of the balloon catheter the catheter tip can be illuminated. When properly positioned in the tube, the light can be seen from outside the ear through the tympanic membrane. The low-cost optical fiber is disposed after use.

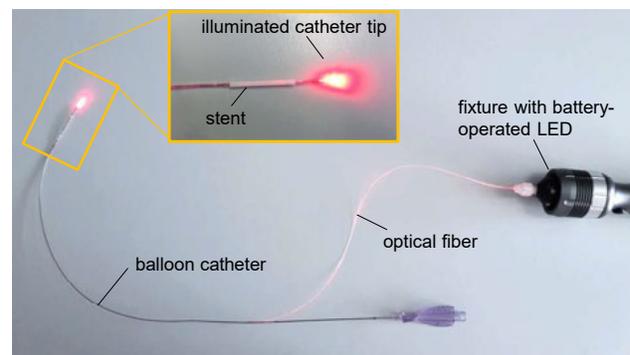


Figure 3: Diaphanoscopy tool advanced through a stent/catheter system

2.4 Human cadaver study

To demonstrate structural access and feasibility of stent implantation in the Eustachian tube, tests were performed on human cadavers. The cadavers were fixated by perfusion and immersion with a 2% formaldehyde and 58% ethanol solution with antibacterial and antifungal additives.

For implantation of the stents, mounted on coronary balloon catheters (see section 2.1), through a transnasal approach the application tool TubaInsert (Spiggle & Theis, Overath, Germany) was used. Controlled by contralateral endoscopy, the application tool was positioned flush with the pharyngeal orifice, angled parallel to the long axis of the Eustachian tube. An applied mark on the catheter shaft allowed an exact positioning of the stent regarding insertion depth with reference to the application tool. Expansion was performed using a manual pump with the balloon catheter's nominal pressure.

Before and after the intervention, cone beam CT images were recorded to evaluate opening of the Eustachian tube by

stent application. Subsequent histological analyses provided information about the resulting cross-sectional geometry of the tube and the implanted stents.

3 Results

With the described method and application instruments the stents could be implanted in the Eustachian tube of human cadavers without difficulties. Diaphanoscopy approach suggests positioning of the catheter in the Eustachian tube (**Figure 4**). Subsequent tomographic and histological analyses confirmed that assumption. The visibility of the stents by means of the integrated radiopaque markers could be proved in postprocedural CT images (**Figure 5**).

In follow-up to the application tests executed histological analyses showed, that the polymeric stents effectuate an opening of the Eustachian tube and adapt to the tube geometry of without generating a complete circular cross-section.

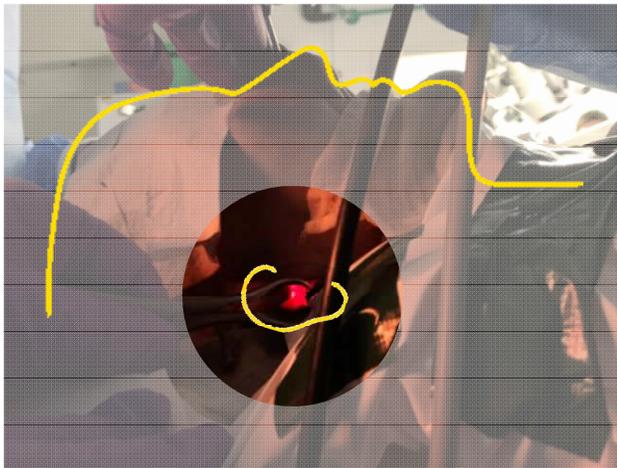


Figure 4: Catheter position control by diaphanoscopy during implantation: light shining through the tympanic membrane of a human cadaver

4 Discussion

With human cadaver studies the access and procedure of stent implantation in the Eustachian tube could be evaluated. Accurate data on the dimensions of the target structure was provided for adaption of stent designs and application tools. Basic limitations include the unphysiological mechanical

response and absence of bleeding or other natural fluids in cadaver models.

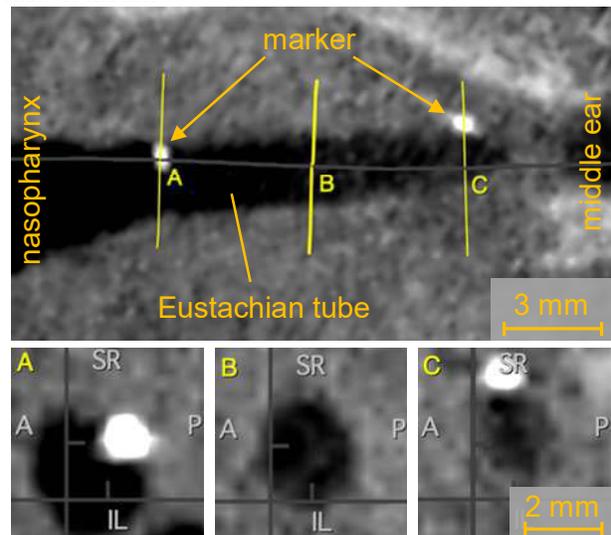


Figure 5: Postoperative cone beam CT images of an implanted polymeric stent (not X-ray visible) with radiopaque markers: longitudinal view (top) and cross-sectional views at marked positions A, B and C (bottom)

Without the radiopaque markers only indirect position control by means of a hollow space generated by the opened tube can be seen in tomographic images. The X-ray markers are an effective instrument to prove exact stent positioning. The integration in the stent by heat input and the subsequent coating ensure safe adherence, but the method might be optimized and automated in further developments to facilitate the manufacturing process. A coating of the stents is planned for prospective preclinical or clinical studies as drug carrier for a local elution with anti-inflammatory or anti-fibrotic effects.

Functionality of the tested diaphanoscopy tool could be demonstrated. Due to the use of a detachable low-cost optical fiber cut to desired length, that can be disposed after every application, the battery operated LED instrument does not come into contact with the operating area. Therefore, requirements to the re-usable instrument are low.

5 Conclusion

Important insights regarding feasibility of stent implantation in the Eustachian tube as well as tools for radiopacity and diaphanoscopy have been gained from the current study. Application of the described stents in conjunction with cardiovascular balloon catheters and a dedicated insertion instrument for balloon Eustachian tuboplasty could be

achieved without difficulties, which demonstrated basic practicability.

Diaphanoscopy facilitates the implantation and provides the surgeon with security regarding correct insertion of the balloon catheter. Radiopaque markers enable the visualization of the stents offering the only control of the actual positioning of the stents.

Once stent designs and application tools are optimized on basis of the findings obtained in cadaver studies, preclinical safety and efficacy studies using animal models will be initiated.

Acknowledgment

The authors thank CORTRONIK GmbH for provision of radiopaque markers. We also thank the Department of Anatomy of the Rostock University Medical Center for preparation of the donor bodies. We also gratefully acknowledge the cooperation with bess pro GmbH in this project.

Author Statement

Research funding: This work was partially funded by the Federal Ministry of Education and Research (BMBF) within the project RESPONSE “Partnership for Innovation in Implant Technology”. Conflict of interest: Authors state no conflict of interest. Informed consent is not applicable. Ethical approval: The research related to human cadaver use complies with all the relevant national regulations,

institutional policies and was performed in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review boards or ethics committees.

References

- [1] Schröder S, Reineke U, Lehmann M, Ebmeyer J, Sudhoff H. Chronic obstructive eustachian tube dysfunction in adults: Long-term results of balloon dilatation eustachian tuboplasty. *HNO*. 2013;61(2),142–151.
- [2] Lenarz T, Wiffling T, Paasche G, Schümann K, Grabow N, Schmidt W, Schmitz K-P, Müller H. Stenting the Eustachian Tube for Treatment of Chronic Otitis Media. Abstract, BMT 2018 - 52nd Annual Conference of the German Society for Biomedical Engineering, Aachen. *Biomedical Engineering/ Biomedizinische Technik*. 2018;63(s1)75–83.
- [3] Pohl F, Schuon RA, Miller F, Kampmann A, Bültmann E, Hartmann C, Lenarz T, Paasche G. Stenting the Eustachian tube to treat chronic otitis media - a feasibility study in sheep. *Head & face medicine*. 2018;14(1)8.
- [4] Grabow N, Bünger CM, Schultze C, Schmohl K, Martin DP, Williams SF, Sternberg K, Schmitz K-P. A biodegradable slotted tube stent based on poly(L-lactide) and poly(4-hydroxybutyrate) for rapid balloon-expansion. *Annals of biomedical engineering*. 2007;35(12)2031–2038.
- [5] Schümann K, Arbeiter D, Grabow N, Schmitz K-P. Method for the improvement of mechanical properties of biodegradable polymeric scaffolds. *Current Directions in Biomedical Engineering*. 2019;5(1)485–487.
- [6] Bayer U, Risch F, Riedmüller J, Quint B. X-ray markers for scaffolds. US 2019/0336310 A1 filed January 8, 2018