



Selection and fabrication of a non-woven polycarbonate urethane cover for a tissue engineered airway stent



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ABSTRACT

One of the major problems in end-stage bronchotracheal cancer is stenosis of the upper airways, either due to luminal ingrowth of the tumor or mucus plugging. Airway stents that suppress tumor ingrowth and sustain mucociliary transport can alleviate these problems in end-stage bronchial cancer. We evaluated different types of polymeric covers for a tissue engineered airway stent. The distinguishing feature of this stent concept is that respiratory epithelial cells can grow on the luminal surface of the stent which facilitates mucociliary clearance. To facilitate growth of epithelial cells at the air-liquid interface of the stent, we developed a polyurethane cover that allows transport of nutrients to the cells. Nonwoven polycarbonate urethane (PCU) covers were prepared by a spraying process and evaluated for their porosity and glucose permeability. Respiratory epithelial cells harvested from sheep trachea were cultured onto the selected PCU cover and remained viable at the air-liquid interface when cultured for 21 days. Lastly, we evaluated the radial force of a PCU-covered nitinol stent, and showed the PCU covers did not adversely affect the mechanical properties of the stents for their intended application in the smaller bronchi. These *in vitro* data corroborate the design of a novel airway stent for palliative treatment of bronchotracheal stenosis by combination of stent-technology with tissue-engineered epithelial cells.

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1. Introduction

Obstruction of the upper airways due to lung cancer can result in life threatening and distressing breathlessness (Herth and Eberhardt, 2016; Wilson et al., 1996). Although the tumor that occludes the airways can be largely resected by bronchoscope-assisted minimal invasive surgery, airway stenting is needed to preserve the respiratory function of patients with end-stage bronchial cancer (Miyazawa et al., 2004; Chin et al., 2008).

A variety of stents are available for application in the tracheobronchial tree, and the biomechanical properties depend on the materials used and how they are constructed (Lee et al., 2010). Silicone stents have been available since the early 1960s but are underused because their insertion requires the use of a rigid bronchoscope (Rafanan and Mehta, 2000). Expandable metal stents have been used successfully to relieve airway obstruction (Coolen et al., 1994). They can be placed via flexible bronchoscopy under local anaesthesia (Mehta and Dasgupta, 1999; Rafanan and Mehta, 2000). For bronchotracheal cancer, the outward pressure of a covered bronchial stent preserves the patency of the bronchotracheal tract at the site of the resected tumor and prevents tumor regrowth into the airway lumen (Weisse, 2011). However, complications have been reported for covered stents such as stent migration and obstruction (Saad et al., 2003; Zakaluzny et al.,

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2003). Moreover, excessive formation of granulation tissue can lead to obstruction of the stent (Madden et al., 2000). Another frequently observed problem for covered stents is mucus plugging, due to impaired mucociliary clearance from the lower airways over the stented bronchial wall (Dutau et al., 2014; Murgu and Colt, 2007). To overcome current limitations of airway stenting for bronchotracheal cancer, we propose a tissue engineered type airway stent that supports regrowth of airway epithelial cells onto the luminal site of the covered stent (Fig 1). The respiratory epithelial layer on the luminal side guarantees improved mucociliary clearance and hence will reduce the risk of mucus plugging (Thiebes et al., 2016). Such an airway stent consists of a nitinol mesh covered with a biocompatible polymeric cover that can support cell adhesion, proliferation and transport of nutrients. Furthermore, the cover needs to withstand the pressure of an ingrowing tumor to prevent restenosis.

In the present study, we evaluated different types of polycarbonate urethane (PCU) nonwoven fabrics for their suitability to serve as cover in the above described airway stent concept. The nonwoven PCU cover was manufactured by a spray coating method that results in a highly porous and flexible material. Different spraying conditions were compared to obtain an optimized cover that supports glucose transport and adhesion and proliferation of sheep respiratory epithelial cells at the air-liquid interface. We used primary sheep epithelial cells for this study in view of a planned biocompatibility and functionality studies in sheep. The dimensions of the upper airways are comparable in sheep and man, thus allowing the testing of stent sizes optimized for human bronchial dimensions. The selected PCU cover was applied onto a bronchotracheal laser-cut nitinol stent and tested for its possible unwanted effects on the stent's mechanical properties.

2. Materials and methods

2.1. Materials

Medical grade polycarbonate urethane (PCU, Carbothane™ 3575A, true density: 1.15 g/cm³) was obtained from Lubrizol Advanced Materials, Inc., USA. All other chemicals were at least from analytical grade. Chloroform was bought from Biosolve, Valkenswaard, the Netherlands. Glucose was bought from Sigma Aldrich.

2.2. Fabrication of PCU covers

The PCU covers were fabricated using a spray coating method (Nadzeyka et al., 2014). Nonwoven PCU covers were prepared by spraying a solution of Carbothane (7.5% w/w in chloroform) onto a rotating spindle (diameter 22 mm, length 20 cm). The spraying unit (Fig. 2) was built in a glove box and consisted of a SATA Mini-jet 3000 spraying nozzle (SATA GmbH & Co. KG, Kornwestheim, Germany), chloroform resistant polyamide tube (KSA, Germany), and a computer driven syringe pump equipped with a disposable syringe (B. Braun, Germany). Spraying settings are listed in Table 1. In order to achieve uniform thickness of the PCU cover, the spraying nozzle was moved constantly along the length of the spindle. The PCU covers were dried in a ventilated oven at 30 °C for at least two hours to evaporate the chloroform, after which the covers were carefully cut from the spindle.

2.3. Characterisation of PCU covers

2.3.1. Morphology and density of PCU covers

PCU covers were examined by scanning electron microscopy (SEM) on a Phenom electron microscope (FEI Company, the

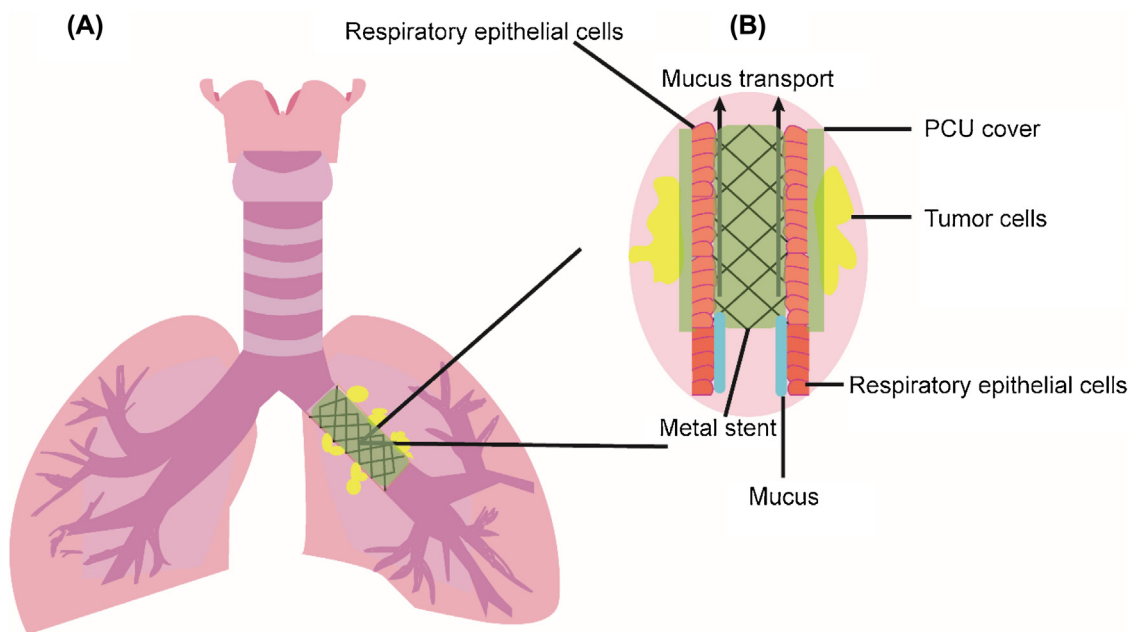


Fig. 1. (A) Schematic picture of the proposed bronchotracheal stent concept. Current therapy for bronchotracheal cancer involves bronchoscope-assisted resection of the tumor. Typically, small tumor nodules will remain after surgery (marked yellow in the figure). After the resection of the tumor, a PCU-covered expandable stent will be implanted in the airways. The outward radial force of the stent will suppress tumor regrowth into the bronchial lumen. (B) Enlargement of the bronchotracheal stent. For existing covered airway stents, mucus plugging at the distal end of the stent is often leading to failure of the stent. The new stent concept supports repopulation of respiratory epithelial cells at the air-liquid interface (orange cells) to improve the mucociliary transport and reduce the risk of stent obstruction. Nutrient transport across the PCU cover is needed to support growth of the respiratory epithelium. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

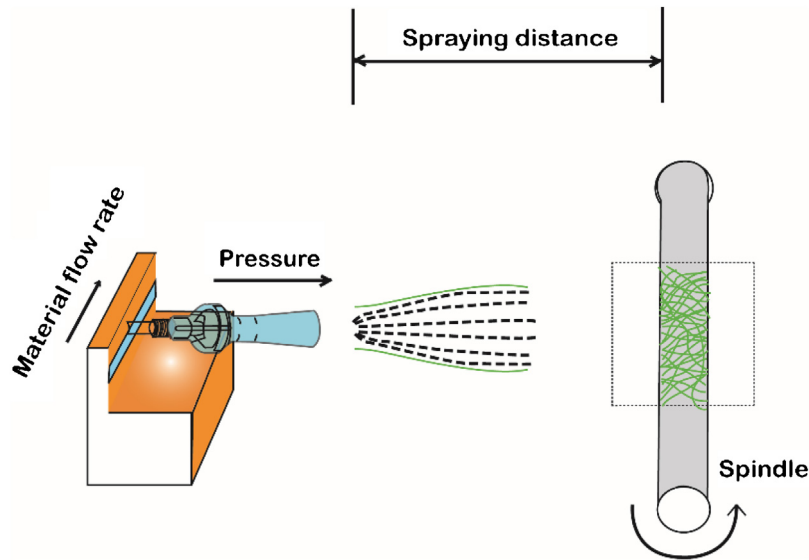


Fig. 2. Schematic display of spraying unit for fabrication of nonwoven PCU covers.

Netherlands). Samples were cut into small rectangle pieces (1 mm × 5 mm) and glued onto 12 mm diameter aluminium specimen stubs (Agar Scientific Ltd., England) using double-side adhesive tape. The cross sections were covered by a fine platinum layer (4 nm) using an ion coater under vacuum. Thicknesses of the PCU covers were calculated with the open source program ImageJ (National Institutes of Health, NIH). PCU cover densities and porosities were calculated using the formulas:

$$\text{Cover density} = \frac{\text{weight}}{\text{area} \times \text{thickness}} \quad (1)$$

$$\text{Cover porosity} = 1 - \frac{\text{cover density}}{\text{true density of PU}} \quad (2)$$

2.3.2. In vitro glucose transport over PCU cover

In vitro glucose transport over the different PCU covers was studied using in-house prepared diffusion cells with two well-stirred compartments separated by the PCU cover. The area of the PCU cover for diffusion was 0.78 cm². Glucose transport was studied at room temperature after filling the donor compartment with 4 ml 5% (w/v) glucose in PBS (pH 7.4, 0.049 M NaH₂PO₄, 0.099 M Na₂HPO₄, and 0.006 M NaCl) and the receptor compartment with 4 ml blank PBS. Glucose concentrations in 20 µl aliquots

from donor and receptor compartments were determined using a commercial glucose meter (AccuChek Sensor Comfort[®], Roche).

Modulated glucose transport over the PCU covers of 100–400 µm thickness was calculated using Fick's equation: $J = -D \times dC/dx$, where dC/dx is the concentration gradient of glucose over the membrane with thickness dx , D is the diffusion coefficient of glucose in the membrane at 25 °C, J is the flux of transported amount of glucose per surface area.

2.3.3. Culturing of respiratory epithelial cells on PCU cover

Primary respiratory epithelial cells were isolated from ovine trachea from sheep euthanized for other purposes at the RWTH Aachen University Hospital Institute of Laboratory Animal Science. Dissected trachea were immediately placed in transport buffer (100 mM HEPES, 140 mM NaCl, 2.5 mM KCl, 10 mM glucose, 1% antibiotic-antimycotic solution, pH 7.4). Respiratory epithelial cells (RECs) were isolated according to a protocol published by Yamaya et al. (1992). Ovine tracheal mucosa was incised longitudinally, mucosa strips were removed and placed into a solution of 1.8 U/ml protease XIV (Sigma Aldrich) and incubated at 4 °C overnight. After removal of the strips and centrifugation, the harvested cells were dispersed in Dulbecco's modified Eagle medium (DMEM), seeded in cell culture flasks and maintained in a humidified incubator at 37 °C and 5 % CO₂. After 48 h, the medium was changed to Airway Epithelial Cell Growth Medium (PromoCell, Germany). Cells were

Table 1

Fabrication parameters and properties of PCU-samples.

Samples	Pressure ^a (bar)	Flow rate ^b (ml/min)	Spray distance ^c (cm)	PCU Sprayed ^d (mg/cm ²)	Cover Weight ^e (mg/cm ²)	PCU recovery ^f (%)	Thickness ^g (µm)	Density ^h (mg/cm ³)	Porosity ⁱ (%)
PCU_A	0.8	2.0	11	8.5	6.30 ± 0.08	74 ± 1	110 ± 7	572 ± 9	50 ± 6
PCU_B	0.8	2.0	23	8.5	5.93 ± 0.11	69 ± 1	240 ± 10	247 ± 4	79 ± 4
PCU_C	1.6	0.5	23	8.5	9.48 ± 0.11	100 ± 1	300 ± 13	316 ± 3	73 ± 4
PCU_D	1.6	0.5	23	12	12.18 ± 0.08	99 ± 1	390 ± 11	312 ± 9	73 ± 3

Surface of the complete PCU cover: 69.08 cm². The true density of PCU is 1.15 g/cm³. Reported values are mean ± standard deviation of three patches of the PCU-covers.

^a Pressure of the carrier gas.

^b Flow rate of the PCU solution controlled by the syringe pump.

^c Spray distance between the nozzle and the spindle.

^d Amount of PCU sprayed as calculated from concentration of PCU, spraying time and flow rate.

^e Cover weights were determined by weighting pieces of 1.85 cm² PCU samples.

^f PCU recovery was calculated from cover weights divided by the amount of PCU sprayed.

^g Thickness was determined from at least 10 different SEM images of the cross-sectioned PCU covers.

^h Density was calculated by formula 1.

ⁱ Porosity was calculated by formula 2 in the methods section.

detached when they reached 70–80% confluency using 0.05% trypsin/0.02% EDTA solution (PAN-Biotech, Germany) and grown onto PCU covers as described below.

PCU samples were fixed in CellCrown™ inserts (Scaffdex, Finland) and placed in a 12-well plate (CellStar®, Greiner Bio-One, Germany). Respiratory epithelial cells of passage 1 were seeded onto the PCU covers with a concentration of 8×10^4 cells/cm² and cultured in submersed condition in Airway Epithelial Cell Growth Medium for 7 days. Next, the culture conditions were changed to an air-liquid interface setup in which the upper compartment of the transwell insert did not contain culture medium. The respiratory epithelial cells were cultured for an additional 21 days at the air-liquid interface in Airway Epithelial Cell Growth Medium supplemented with retinoic acid (50 nM, Sigma-Aldrich, Germany; protocol from PromoCell). Medium was changed every other day. At the end of the 28-day culture, cells were fixed with paraformaldehyde for 30 min, washed three times with PBS, after which nuclei were stained with 4' 6-diamidino-2-phenylindole (DAPI; Sigma Aldrich). Images were taken with Zeiss Zoom.V16 and ZEN pro software (2012, blue edition).

2.4. PCU-covering of nitinol stent

Nitinol airway stents (15 mm diameter; 30 mm long) were designed and laser-cut from a single nitinol tube of 5 mm outer diameter (OD) and 0.23 mm thickness as described elsewhere (McGrath et al., 2014). The stent was placed on the rotating spindle and fixed at both ends with non-adhesive tape. At each side of the

stent, 5 mm of the nitinol was covered by the tape to allow for non-covered ends that facilitate the anchorage of the stent into the bronchial wall. A nonwoven PCU cover was applied as described in Section 2.2 according to setting B (2 ml/min spraying solution; 0.8 bar; 23 cm distance). After drying of the coating as described above, the tape was carefully removed from the masked ends of the stent.

2.5. Stent radial force testing

Radial force testing was carried out on a bare and a PCU-covered stent on an 8-faced crimping head (RCM-H60, MPT Europe) connected to a Zwick uniaxial testing machine (Zwick 7025-3, Zwick, Ulm, Germany). Stents were crimped from their free diameter (15 mm) to a constrained diameter of 7.5 mm (100% crimped state) at a rate of 0.06 mm/s at 37 °C. After crimping, the stents were allowed to expand to their original diameters at the same rate. Testing a stent in this way replicates the loading it undergoes when inserted into a delivery device (crimping step) and develop into an airway (expanding step).

3. Results and discussion

3.1. Characteristics of the PCU covers

Polycarbonate urethanes are used in a wide variety of medical devices such as catheters, heart valves and coatings (Davis and Mitchell, 2008) as well as for drug delivery applications (Cherng

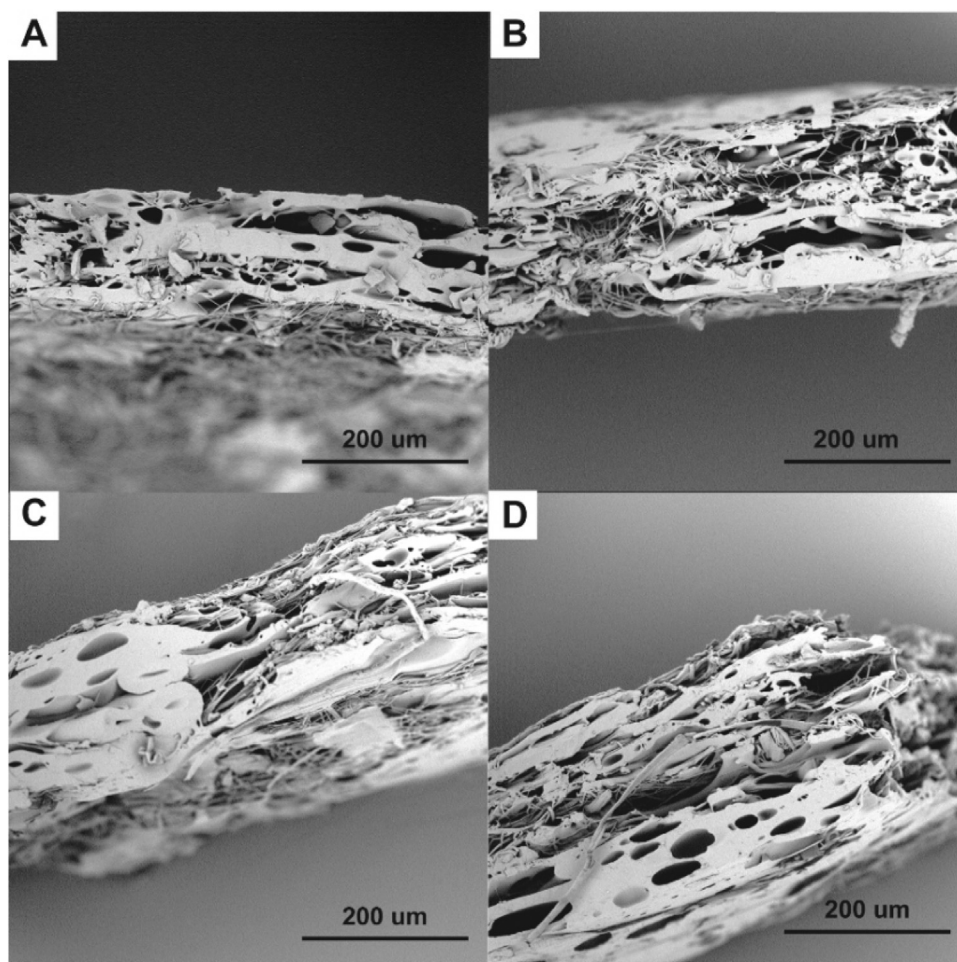


Fig. 3. SEM pictures of cross-sections of the PCU covers PCU_A (A), PCU_B (B), PCU_C (C) and PCU_D, respectively. Magnification $\times 600$.

et al., 2013). We made nonwoven PCU covers as listed in Table 1 by spraying a diluted PCU solution onto a rotating spindle. Several settings of the spraying unit were varied, such as spraying pressure, flow rate of the PCU solution and the distance between the spraying nozzle and the rotating spindle. Covers A–C were sprayed with 6 ml of polymer solution while Cover D was sprayed with 10 ml, corresponding to 8.5 and 12 mg PCU/cm² on the spindle. Cover weights determined after drying of the material nicely correlated with the amount of sprayed PCU, amounting to a recovery of 70–100% of the PCU for either high flow rate/low spraying pressure (A, B) or low flow rate/high pressure (C, D). Thicknesses of the PCU covers were determined from SEM photomicrographs taken from cross-section of the materials (see below). Roughly, the thickness of the 4 prepared covers ranged from 100 to 400 μ m. Densities and porosities of the covers were calculated from cover weight and SEM cross-section thicknesses. The porosities of the covers ranged from 50 to 79%, which indicates that the non-woven materials had a high porosity with likely interconnected pores which in principle should allow transport of nutrients.

Fig. 3 shows SEM images of the cross-sections of the PCU covers. These photomicrographs clearly demonstrate the porous structure of the nonwoven materials. The thicknesses of the PCU covers listed in Table 1 were measured in ten different SEM images of the developed covers. For all PCU covers, different types of porosity can

be observed. Larger cavities most likely reflected porosity between the strands of deposited material. In addition, smaller pores within the polymeric material were observed. Although it is difficult to judge whether the above calculated high porosities of up to 79 % were correct, the images showed that the covers form a connected layer, which was also observed macroscopically (data not shown).

3.2. Glucose transport across the PCU covers

We measured glucose transport over the PCU covers in a two-compartment diffusion cell with stirred chambers filled with either PBS (receptor chamber) or PBS with glucose (donor chamber). It is assumed that glucose transport occurs via buffer-filled pores of the nonwoven PCU covers which means that under steady state conditions the glucose transport can be described by Fick's first law of diffusion as mentioned in 2.3.2. Fig. 4A shows that equilibrium between the two compartments is reached in about 20 h for PCU_A membrane (110 μ m thickness). This figure also shows that the data can be well fitted using a diffusion coefficient of 1×10^{-6} cm²/s, which is lower than the D_{glucose} in water (6.7×10^{-6} cm²/s) (Flynn et al., 1974). Fig. 4B shows that for PCU_B, which is about two times thicker than PCU_A, equilibrium is reached within 1 h. This points to a higher D_{glucose} in this cover which can be explained by its higher porosity (79% of PCU_B and 50% of PCU_A). Fig. 4C shows that for PCU_C (300 μ m) the time to

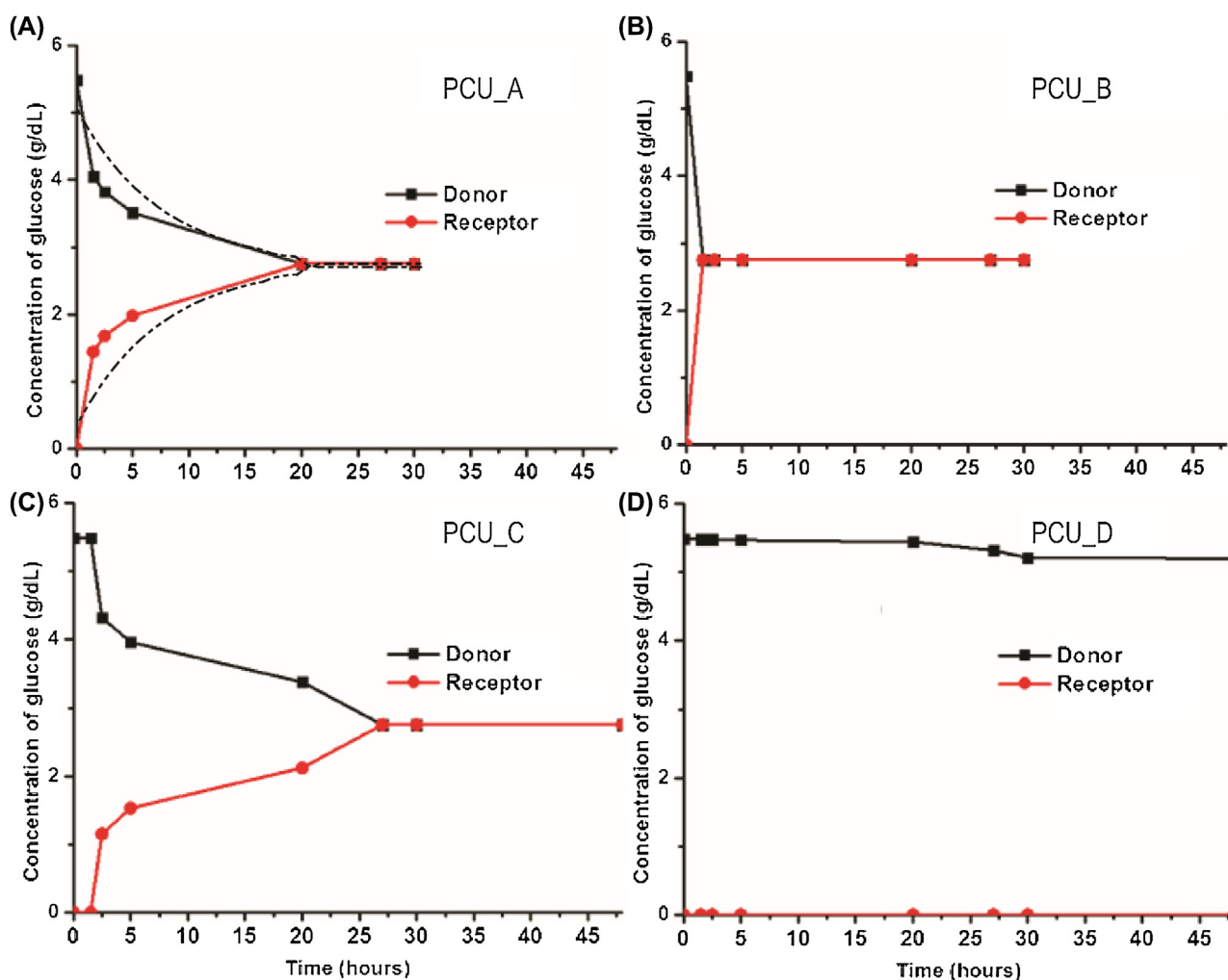


Fig. 4. Glucose transport across polyurethane membranes PCU_A (A), PCU_B (B), PCU_C (C) and PCU_D (D). Black line: concentration of glucose in donor chamber, red line: concentration of glucose in receptor chamber, N=3. The dotted lines in A shows the calculated transport assuming $D_{\text{glucose}} = 1 \times 10^{-6}$ cm²/s. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

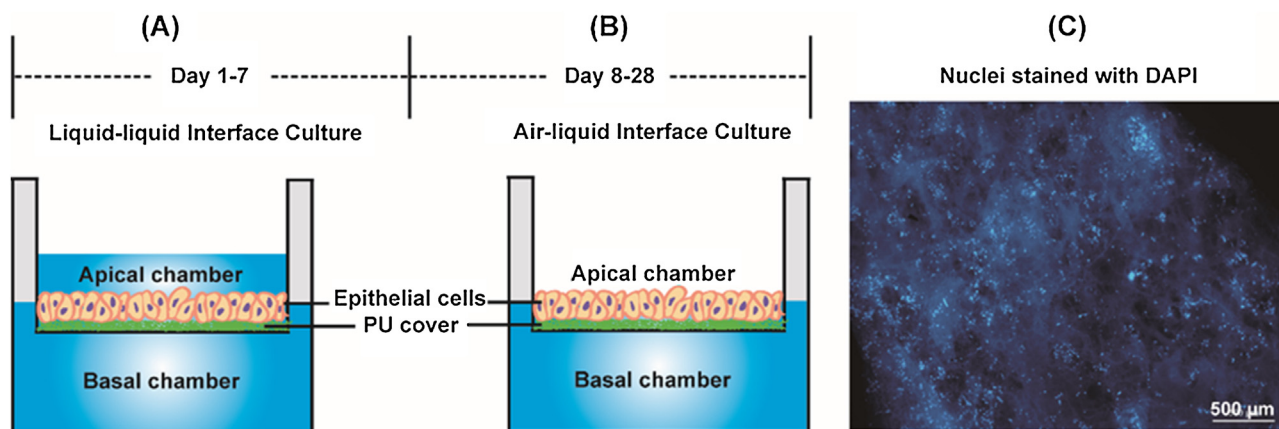


Fig. 5. Culturing of respiratory epithelial cells on PCU covers. (A) Primary sheep epithelial cells were first cultured onto PCU covers under immersed conditions. (B) PCU-attached epithelial cells were grown at air-liquid interface by applying differentiation medium only in the basal chamber. (C) DAPI-staining of respiratory epithelial cells grown for 21 days at air-liquid interface of PCU_B.

reach equilibrium was 27 h which is similar to that for PCU_A. Obviously, the higher porosity compensates the longer diffusion distance. Finally, Fig. 4D shows that PCU_D is essentially impermeable for glucose despite its high porosity. Likely the pores are not interconnected and therefore glucose transport does not occur. A plausible explanation is that the sprayed PCU_D material has merged into a closed layer once the material has attached to the spindle, a process that can still occur while the polymer is flexible and not fully returned to its rubberness state. Although the evaporation of the carrier solvent is supposed to occur before the sprayed droplets deposit onto the spindle, trace amounts of chloroform will still be present until the PCU cover has hardened out. Slower evaporation of chloroform during the hardening phase will favor fusion of individual polymer strands into a closed layer. It is fair to expect that this will occur most in PCU_D, since this cover contains the highest aspect ratio (i.e. a 4× higher layer as compared to PCU_A) and evaporation can only occur at the surface of the cover. Apparently, the denser material of PCU_D had formed a closed structure without an interconnected pore network while such structures were still present in PCU_A–C. In view of the need for efficient nutrient transport over the PCU cover, we selected cover PCU_B for further testing of respiratory epithelial cell growth.

3.3. Culturing of respiratory epithelial cells on PCU cover

Tracheal epithelial cells have an important role in the clearance of mucus from the lungs and small bronchi. Fully covered airway stents suffer from mucus plugging since the mucus transport is impaired over the surface of the stent. Repopulation of the stents

surface with epithelial cells – as proposed presently – may alleviate this problem. It is therefore important that respiratory epithelial cells can grow at the air-liquid interface on top of the PCU covers. We evaluated adhesion and proliferation of respiratory epithelial cells under such conditions *in vitro*, using epithelial cells isolated from sheep trachea. After initial culturing of the isolated cells under immersed conditions to allow attachment and proliferation of the cells on the polymeric material (Fig. 5, panel A, day 1–7), the primary cells were grown for another three weeks at air-liquid interface in well-plate inserts. Since the cells were cultured on top of PCU cover, they relied fully on transport of nutrients over the nonwoven material (Fig. 5, panel B, day 8–28). Fluorescent images of DAPI-stained cells at day 28 showed that respiratory cells had evenly distributed over the surface of the PCU cover during the 21-days of air-liquid interface culture (Fig. 5, panel C). This result shows that permeability of the cover is sufficient, enabling transport of nutrients and most likely also of growth factors and other molecules that are needed to nourish respiratory epithelial cells.

3.4. Fabrication of PCU-covered bronchotracheal stent

A laser-cut stent was designed using finite element methods (McGrath et al., 2014). This stent of 15 mm OD was designed to provide a radial force of approximately 11–20 N when implanted in a 12 mm bronchus, based on benchmark testing of commercial tracheobronchial stents in the radial force testing apparatus described in the methods section. Fig. 6 shows the appearance of the bare metal stent and its PCU-covered counterpart. The last 5 mm of each end of the metal stent stucts was left bare to allow

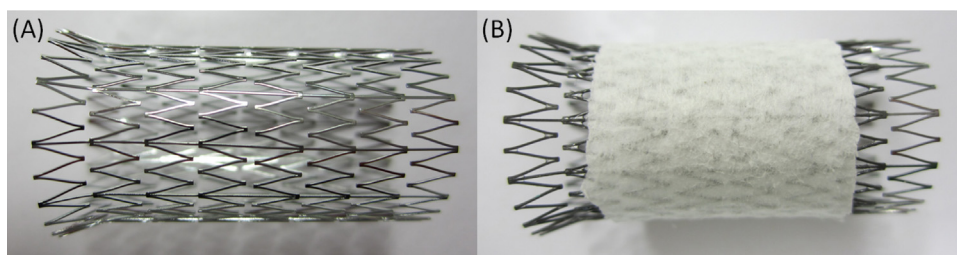


Fig. 6. Images of the fabricated bare laser-cut metal stent (A) and PCU_B covered metal stent (B). The size of both stents was 15 mm × 30 mm (outer diameter × length), the ends of the PCU_B covered stent were left uncovered to prevent migration of the stent due to better adherence to the tracheal wall.

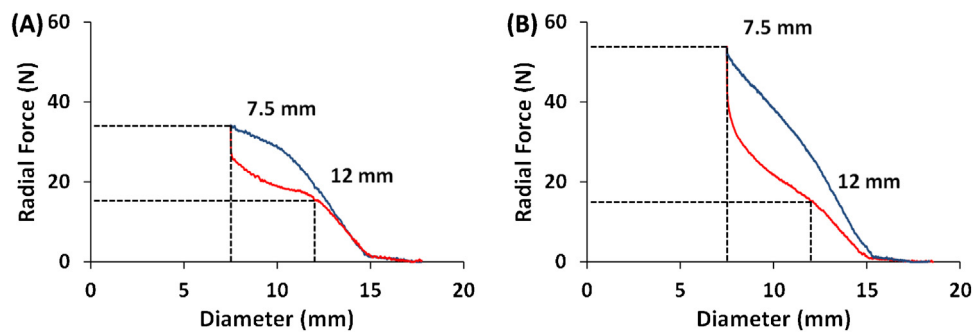


Fig. 7. Radial force curve of bare metal stent (A) and PCU_B-covered metal stent (B). The upper blue line refers to the loading cycle and the lower red line refers to the unloading cycle. The intersection of a dashed line corresponds to the radial force of the bare metal stents and PCU_B-covered metal stent at the outer diameter of 7.5 mm and 12 mm. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the stent to adhere firmly into the bronchotracheal wall, which will ensure that the stent remains in the desired position. This hypothesis and the biocompatibility and functionality of the discussed airway stent are currently tested in healthy sheep, in a study design that will follow the fate of the stent up to 6 months after implantation.

In the present study, we evaluated the effect that the cover has on the radial force of the laser-cut stent in an experiment that represent the crimping of the stent and its deployment out of a suitable sized delivery system. The results of the radial force tests are shown in Fig. 7. The coated stent was successfully crimped to a diameter of 7.5 mm, which represents the inner diameter of the intended delivery device. The coating caused a significant increase in the radial resistive force (RRF) (the loading cycle highlighted in blue in Fig. 7) of the stent, which resulted in a difference of 19 N between the stents at maximum crimp (7.5 mm). The chronic outward force (COF) (the unloading cycle highlighted in red in Fig. 7) of the stent is also increased by the coating, but to a lesser extent than the RRF. This is particularly evident at 12 mm unload (a typical deployment diameter for a 15 mm stent assuming a 20% oversizing) where the COF is 15 N for both stents. The COF of the coated stent at a 20% oversizing remained mid-way between the range observed (11–20 N) for commercial tracheobronchial stents. The higher RRF for the coated stent may reduce the risk of stent migration when the airways contract during coughing. A more detailed analysis of the effect that coatings can have on stent response can be found in other studies (De Bock et al., 2013; McGrath et al., 2016).

4. Conclusions

In this study, polycarbonate urethane was spray-coated onto a rotating spindle to form porous non-woven covers. The densities and porosities were calculated according to the practical data and the formulas. PCU_B showed lowest density and highest porosity, the glucose transport across the PCU covers revealed that the PCU_B had highest permeability of glucose (the concentration of glucose in the donor and receptor compartment reached equilibrium in 1 h). Importantly, PCU_B showed good cytocompatibility with respiratory epithelial cells. In conclusion, we have developed a nonwoven PCU cover for airway stents that can support adhesion and proliferation of respiratory epithelial cells at air-liquid interface. Such an improved airway stent concept can solve current problems with airways stents such as impaired mucus transport. Currently, we are evaluating the biocompatibility and functionality of the airway stent in sheep and in future studies

we will investigate whether anticancer drugs can be incorporated in the polymeric cover.

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