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Research Article

Rapid Prototyping Techniques for Manufacturing Fully Customized Airway Stents

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Abstract

Currently available airway stents are made for average airways. They are circular in cross-section and have the same radial expansion force along their lengths. Customized stents that match the individual airway shape and biomechanical requirements can be manufactured by additive rapid production techniques such as 3D printing. Silicone and resin printers are very expensive and the currently available materials are not approved for implants. Fused deposition molding (FDM) from elastic filaments is feasible for printing anatomically shaped prostheses with thin walls. As it is impossible to print mesh type stents from elastic materials with these techniques, we have combined the additive technique of FDM printing with the subtractive technique of laser ablation. Thinning or cutting out FDM printed stents enables the adjustment not only of all shapes and dimensions but also the local hoop strengths and can determine which part of the affected airway shall be completely covered and which part can have free zones.

This helps to preserve mucociliary clearance and mucosal blood perfusion. In a third additive step (e.g. dipping or electro-spinning) these stents can be covered or coated with active agents making them drug release devices. The focus of this paper is to highlight the concept of producing anatomically and biomechanically optimized airway stents in the shortest possible time by combining FDM printing with flexible filaments, along with subtractive laser ablation, and tertiary techniques such as electro spinning with anti-infectious or anti-proliferating drugs.

Keywords: Customized airway stents; 3D printing; fused deposition molding; laser cutting

Introduction

Airway stents can provide instant and lasting relief of dyspnea for patients suffering from airway compression or airway wall destruction [1,2]. However, despite the fact that they have been used widely in clinical practice for more than thirty years, currently available airway stents still create significant side effects and problems [3,4]. Whether they are made of metals or polymers,

adverse stent-tissue interactions are in part attributable to material properties but are mainly due to biomechanical problems [5]. Almost all commercially available stents are cylindrical and have the same radial expansion force along their lengths [6]. These stents which are circular in cross-section cannot match airway structures, particularly of diseased patients. Whether it has to deal with a lateral tumor compression or a triangular shaped benign stricture, a cylindrical stent can only be a compromise. Irregular and asymmetrical compressive forces are not counteracted by a simple stent with its uniform expansion force. Furthermore, straight stents are suboptimal in curved airways and abrupt changes of diameters cannot be compensated.

Stents are held in place by friction from pressure against the airway walls. Localized pressures and micro-movements promote growth of granulation tissue, especially at the edges of airway stents. Oversizing impairs tissue perfusion and leads to necrosis, while undersizing results in the risk of stent migration [7,8]. Despite great progresses in material developments, stents remain foreign bodies. Impaired mucus clearance and colonization of the stent material often causes mucostasis and chronic infections [9-13]. Approaches to overcome these problems include: customizing stents for shape [14,15]. Making biodegradable stents that get eventually absorbed or integrated into the airway walls [16-23] or making stents that release antimicrobial and anti-proliferative drugs [24-29]. The ideal stent would have an individually optimized shape and appropriate local expansion force, would be highly biocompatible, discourage infections and the formation of granulation tissue, and disappear when no longer needed [30,31].

Newly developed additive manufacturing techniques such as 3D printing with flexible polymers enable the production of individualized stents with improved mechanical properties. Several groups have produced customized stents either by direct printing [32-34] or by printing casts for silicone molding [35-37]. For regulatory reasons molded silicone stents are easier to establish. Medical grade silicone is approved by regulatory bodies, has almost perfect biomechanical properties and can be easily sterilized. The disadvantage is that it can be molded but cannot be printed with appropriate surface qualities using low cost printers [38,39]. The recently presented DLP silicone printers cost more than a hundred times typical FDM printers that use filaments. The ordering process of silicone molded stents takes time and the authors have lost patients on the waiting list. For speed and versatility, direct printing with affordable printers would be favorable. We have recently demonstrated that a customized airway stent can be produced on site with a modified 3D printer from flexible polyurethane within a few hours [31]. Ideally, some parts of the stent should have very thin flexible walls resembling the posterior wall (pars membranacea) of the trachea while other parts should be stable and strong enough to withstand a tumor compression or a circular stricture [40].

Theoretical Considerations and Practical Approaches

Stent planning and designing

For stent planning, we always start with bronchoscopy and Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) of the airways [41]. At first sight it seems reasonable to use a virtual bronchoscopy technique to transfer the images into a printing file [42]. The results are models with narrowing and distortion of the diseased airways. These casts or prosthesis reinforce better anatomical understanding and aid complex thoracic surgeries [43-47] and are also very helpful in interventional procedural planning [35,38,39,41,48-52]. However, the models do only reflect the actual situation but not the desired one. A stent that would simply match the narrowed airway would not improve the condition after deployment. Furthermore, it is important to consider the dynamic airway. Whenever possible, we have the patient perform different breath maneuvers: normal breathing, followed by forced expiration and finally coughing. We also ask the patient to flex and extend the head as the trachea changes its length by almost 30% depending on the head position. CT images are ideally collected with high speed machines under Valsalva and Muller maneuvers. The DICOM files are loaded into a segmentation program (e.g. 3D Slicer, NIH) [48].

Cuts from various levels are exported into drawing, tracing and CAD programs. The most important step is to modify the model of the actual airway towards the desired end-result. The placeholder shall dilate the narrowed area and keep it patent. The expansion force of the stent must be sufficient to open the stenotic area without rupturing the tissue and it shall not overstretch the unaffected part. After tracing the airway outlines we transfer them into splines. The vertices of these splines of the stenotic areas are dragged and stretched to dimensions that seem reasonable. In practical terms, these are compromises between the actual (severely narrowed) and the ideal (fully normal) shapes and areas. Next, the pile of slices is transferred into a solid body. Currently, we use 123 Design and Fusion 360 (Autodesk, San Rafael, USA). These CAD programs have convenient loft modules enabling the design of smooth transitions between slices. Depending on the biomechanical requirements and the printing material, local wall thicknesses are adjusted. Figure 1 illustrates this approach. Slicer programs are used to transform the CAD stl-files and create g-codes for the printing machines.

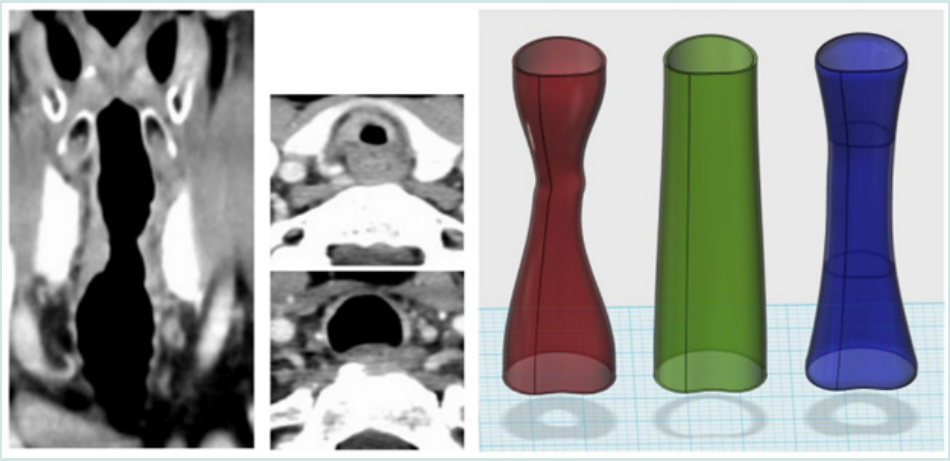

Figure 1: CT images of tracheal stenosis demonstrating round and horseshoe shapes at different levels. Customized stent construction based on patient`s CT image and bronchoscopic findings. The stent dimensions (right) are structured between the actual (left) and the ideal values (middle).

The two basic additive production techniques for stent printing are stereo-lithography (SLA) and fused deposition modeling (FDM). SLA printers use liquid resins that are polymerized by illumination with laser beams or other high-power light sources. At present, the materials that are available are limited, especially when high flexibility is required. Another problem is the potential cell toxicity of the chemicals. The variety of filaments for FDM printers is much greater. Polyurethanes and soft poly-lactid mixtures with material properties similar to silicones are widely used for rapid prototyping. After several years of experiments, we have opted for a modified FDM printer with a printing nozzle diameter of 0.15 mm (Krautwasser & Wenger, Konstanz, Germany). Figure 2 shows that it is possible to print individually shaped stents from flexible material such as soft PLA, TPE or polyurethane with wall thicknesses of 0.6 mm.

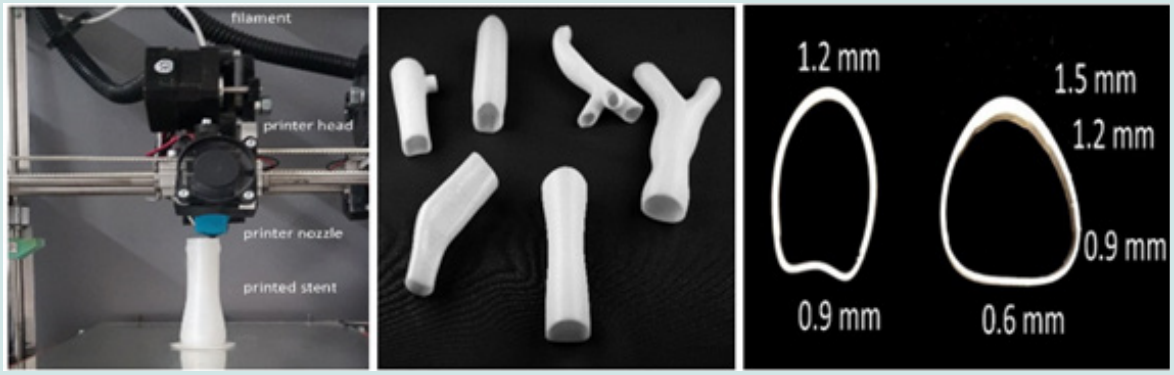

Figure 2: Stents are printed from flexible polymer filaments with a modified 3 D printer. Stent wall thickness can be varied influencing the local recoil and dynamic behavior.

Stent design

Stents must counteract tumor compression and must prevent tumor ingrowth into the airway lumen. If there is intraluminally growing cancer tissue, a stent wall or a stent cover acts as a necessary barrier to maintain airway patency. In cases of extrinsic compression or benign strictures, it is debatable whether a stent must be always completely covered. There is a risk that granulation tissue can grow through gaps in the stent structure. On the other hand, impaired mucus clearance is a most relevant clinical problem in stent patients and more covered mucosa usually creates more retained secretions. In order to maintain ciliary clearance a stent that only covers that part of the airway wall that is mostly affected while leaving healthy mucosa uncovered would be desirable. Another aspect is the stent-tissue interaction. The expansile force of a stent is distributed over its surface. A wire stent with meshes has a relatively low contact area (wire thickness) resulting in high localized pressures on the mucosa (Figure 3a). These pressures exceed the bronchial mucosal pressures, impair microcirculation and favor the selection and proliferation of fibroblasts which are less demanding of blood and oxygen supply. Granulation tissue formation is a typical finding at contact spots between wire ends and mucosal tissue. According to these theoretical considerations we have tried to design individualized stents with partly solid and partly mesh-type walls. The struts should be broader than metal wire filaments, have a higher contact area and should have smooth edges (Figure 3b). However, braided structures or very thin walls are almost impossible to print from rubberlike material with fused filament deposition printers. Using flexible resin with photo-polymerization printers we could produce detailed mesh-type stents (Figure 4a) but failed when we tried to print stents with zig-

zag patterns from flexible filaments with any of our FDM printers (Figure 4b) During the printing process the flow of the soft melted material could not be controlled well enough resulting in stringing and collapse of the structures.

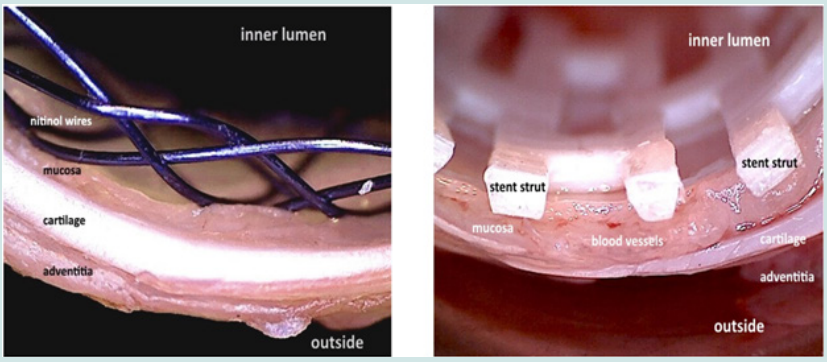

Figure 3: Thin wires of braided metallic stents (left) can severely impair microcirculation, a mesh-type polymer stent can be designed with broader struts preventing high localized pressures on the mucosa (right).

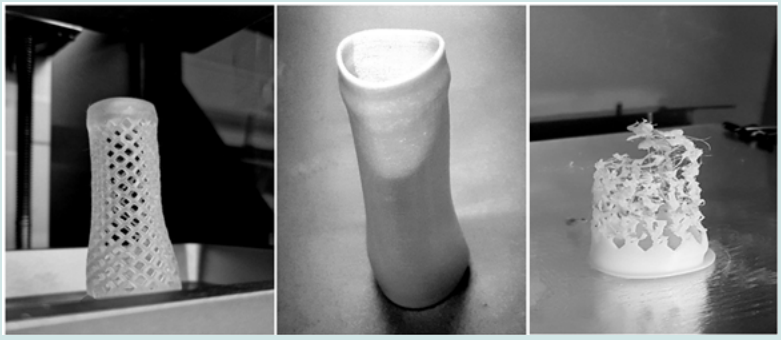

Figure 4: Flexible mesh-type stent printed with photo-polymerization resin printers (left). Straight full-wall stent from flexible filaments directly printed on FDM printers (middle). Mesh-type stents could not be printed with flexible materials on FDM printers (right).

Stent production

After various attempts to produce flexible mesh-type stents with our printers had failed, we developed a combination technique. First, we use FDM printers to print the anatomically matching stents with optimized shapes and wall thicknesses from soft filaments. Next, a laser is used to cut out parts of the printed walls. The printed stents are mounted on a rotating axis and tessellation patterns are cut with a laser. Our laser is based on a 40 Watt, water-cooled CO_2 laser. We modified it with two extra axes controlled by stepper motors. Experimentally, we found energies of 25 Watt with travelling speeds of 220 mm/ sec ideal to cut tessellations out of soft PLA stents with wall-thicknesses between 0.6 and 1.2 mm (Figure 5). While the cuts are sharp and precise, the edges of the cut-outs are smooth. Dipping the stents in dichlormethane (chloroform) for 30 seconds resulted in further smoothening of the surface and the edges. By combining FDM printing and laser cutting we could produce anatomically and biomechanically optimized mesh-type stents from flexible soft PLA with the same quality as photo-polymerization produced stents from non-flexible materials.

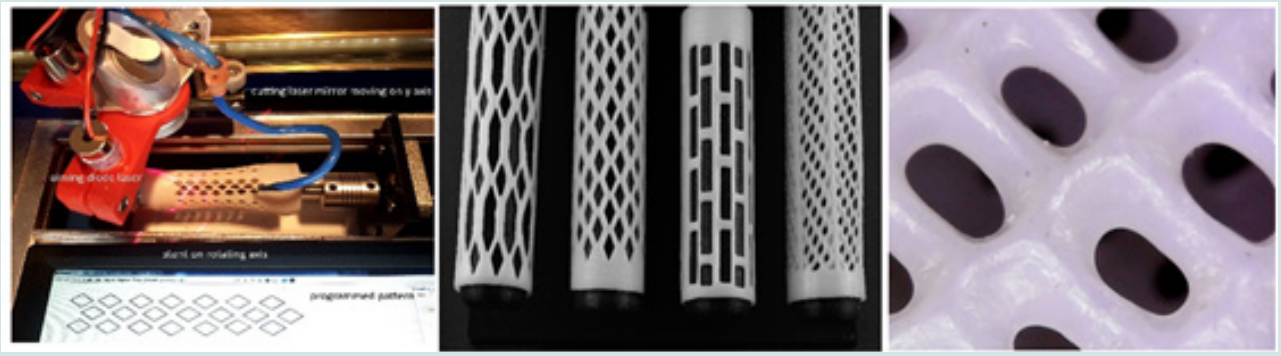

Figure 5: Laser ablation and cutting an FDM printed stent mounted on a rotating rod (left). Any tessellation pattern can be created (middle) with smooth edges (right).

In Vivo Experiments

After acquisition of chest tomographies of pigs, individualized stents were designed and manufactured for three animals. A branch for the tracheal "pig" bronchus was printed in order to avoid migrations. Construction, printing and cutting was accomplished within 24 hours. Cleaning and sterilization took another day and then the stents could be inserted in the animals. We used standard instruments, rigid bronchoscopes and a jet ventilator. An optical forceps was used to turn the stents and position the side arms into the tracheal bronchus. Endoscopic video sequences showed perfect matches between the airway walls and the stents of the three animals. The flexible structures adapted well to the luminal changes during breathing and coughing. When the stents had to be removed on day five (according to the original protocol which had been approved by the Veterinary School of Medicine, University of Thessaloniki), some mucus had accumulated, dominantly on the posterior wall of the stents. No other side effects were observed. The mucosa looked almost normal, no tissue damage was visible. We are currently performing long-term experiments to assess possible chronic effects (Figure 6).

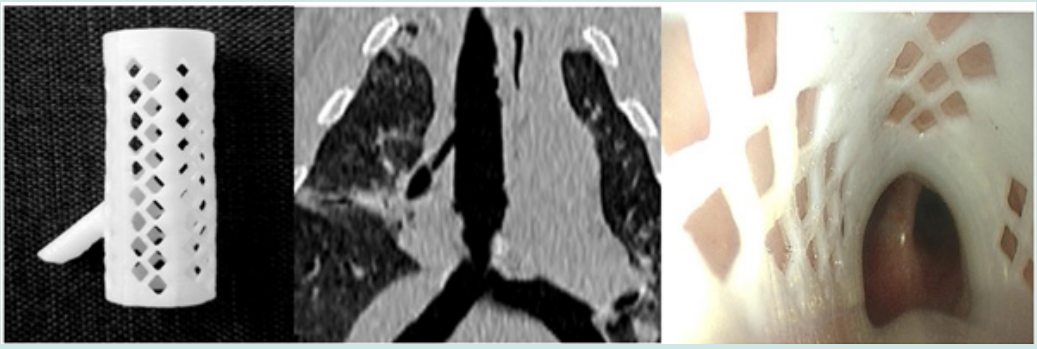

Figure 6: The implanted stent with the pig bronchus arm matches perfectly the individual anatomical situation.

Biomechanical Adjustments

The expansion force (hoop strength) of any stent depends on the elastic modulus of the material, the wall thickness and the design. The described technique enables not only to adjust the overall expansion force of the whole stent but also to tweak it locally along the length and the circumference. A further option is to vary the recoil by changing the ablation parameters with the laser-cut patterns. We used a self-built compression machine to measure the stent mechanics. The methods are described elsewhere [5]. Figure 7 shows stress-strain curves of printed stents with identical diameters and lengths but different tessellation patterns. Commercially available Dumon silicone stents (Novatech France) and Polyflex stents (Boston Scientific, USA) are added for comparison. The graph proves that it is possible to achieve any expansion force by selecting the appropriate tessellation pattern. Of course, there are limitations as the remaining struts must be broad enough to avoid impairment of the mucosal micro-circulation. Pattern dimensions and depths of laser ablation determine the expansion force of the stent. The FDM printed stent can be modified to achieve hoop strengths in the range of commercially available stents. Polyflex stent (Boston Scientific) and Dumon stent (Novatech) shown for comparison.

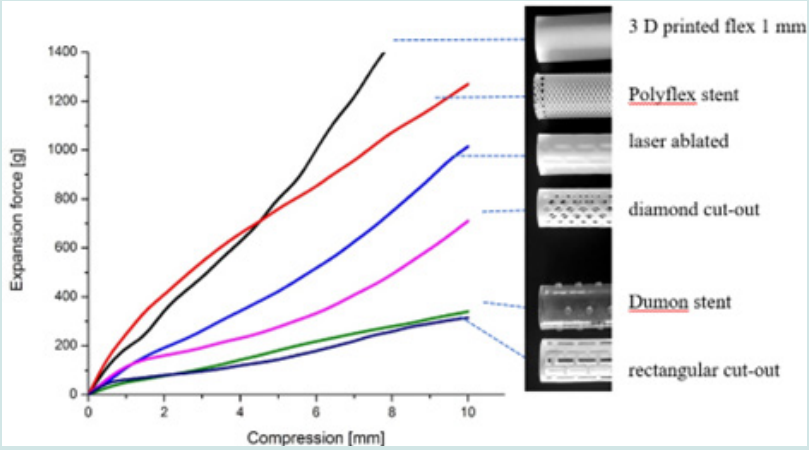

Figure 7: Stress-strain measurements of printed stents. Pattern dimensions and depths of laser ablation determine the expansion force of the stent. The FDM printed stent can be modified to achieve hoop strengths in the range of commercially available stents. Polyflex stent (Boston Scientific) and Dumon stent (Novatech) shown for comparison.

Stent Modification

Following the subtractive step of laser ablation, these biomechanically optimized stent structures can be covered or coated with degradable material, anti-infectious or anti-proliferative drugs. Various additive techniques such as dipping, electro-spraying or electro-spinning have been successfully used to produce individualized multifunctional stents. We have built an electro-spinning unit to cover our mesh-type stents. Stent materials are dissolved in dichlormethane and methanol. Drugs such as Mitomycine C are added and the solution is applied with a computer-controlled syringe pump in an electric field of 18 KV at a distance of 15 cm to the stent on a fast-rotating grounded rod. Depending on the parameters, films or fibers are created, covering the stent surface (Figures 8 & 9).

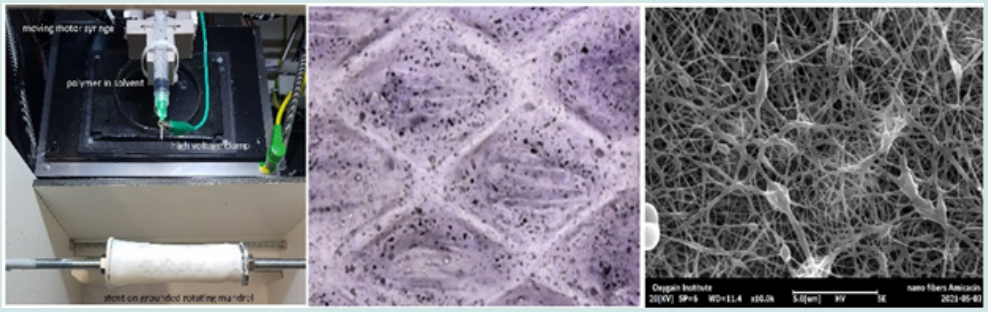

Figure 8: Electro-spraying or electrospinning the laser printed and laser-cut stent with drug releasing coatings (left). Semi-porous film of degradable polymer containing Mitomycine (light microscopy, middle) or nano-fibers with antibiotics (scanning electron microscopy, right).

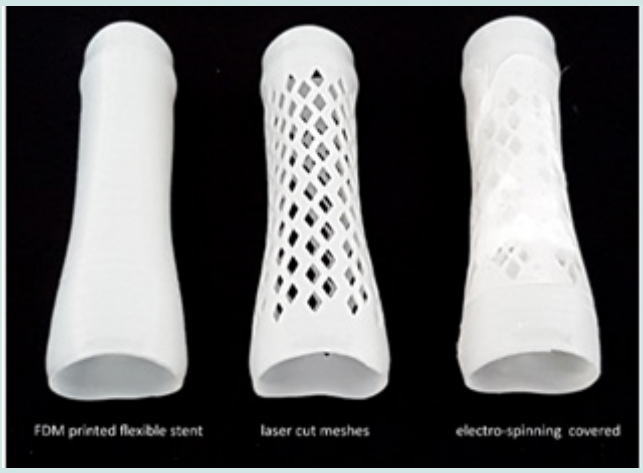

Figure 9: Three step manufacturing of flexible, anatomically shaped, mesh-type stent with drug eluting cover.

Discussion

The presented work demonstrates possible strategies of producing biomechanically and biologically optimized airway stents that could overcome disadvantages of currently available stents. These individualized stents are produced by a combination of additive and subtractive 3-D printing techniques, involving

a. Shaping stents to the individual airway and modifying them to the desired final result

b. 3D printing these individualized stents from flexible materials with affordable printers

c. Tessellating the stent by laser cutting to achieve appropriate expansile force in individual segments of the airway, while avoiding undue airway pressures, while maximizing muco-ciliary clearance and circulation

d. electro-spinning and electro-spraying techniques to add drugs with anti-microbial or anti-proliferative effects.

There is a pressing clinical need for individualized airway stents and clinicians are demanding stents with less side effects. Getting a perfectly matching stent that could even release drugs for a specific patient within a few days is very attractive. Several attempts have been made to turn airway stents into drug releasing devices by either incorporating anti-proliferative substances into the material itself or by modifying a covering. Recently techniques have been developed to even modify silicone stents so that they release paclitaxel in a predictable manner for suppressing granulation tissue formation [53]. More established techniques use soluble medications added to the coating of polymeric stents. This can be done e.g. with stamping of PLA with drugs [54]. We opted for electrospinning which has been used for the coating of vascular stents [55]. The polymer filaments that we are using for the stent body production can be dissolved together with drugs such as mitomycine to make coating fluids that can be electro-spun. We also tried mixing drugs in water-soluble polyvinyl alcohol (PVA) as coating material. As PVA is dissolved by water in bronchial fluid,

this could be used as short acting anti-infectious coverings of stents. This could help to avoid the spread of infections when a vulnerable mucosa gets harmed during the stent placement procedure. It will require a lot of experimental work to determine the ideal formulation and we only wanted to demonstrate the feasibility of this approach to further individualize an airway stent for a specific patient. We have used a CO2 laser to cut out parts of our stents and modify their biomechanical behaviour. Mathematical models have been developed that could help to optimize these patterns for specific needs [56].

So far, we have only tried to influence the local expansion force with laser cutting, but it might be possible to improve the folding and crimping ability of airway stent and facilitate their implantation. Our experiments demonstrate a proof-of-concept to produce an anatomically, biomechanically and drug-eluting airway stent with low-cost equipment in a very short time. It is important to note that the currently available printing materials do not have approval for implants. Customized molded silicone stents have already limited approval but there are still big hurdles, e.g. FDA has only cleared bifurcated airway stents. Getting CE marked customized stents can still take weeks which makes this approach unfeasible for dyspneic patients. On occasion of this years Formnext fair, 3D silicone printers have been announced for next year for general use. However, it may take years until they may get approval for medical purposes. The most sophisticated SLA silicone printer by Spectroplast, Zurich, Switzerland is far more expensive than the printers that we have used and their produced implants have approval for 28 days inside human bodies.

The medical grade filaments from polyurethane or soft PLA that we have tried are approved for skin contact, not for implantation. However, this does not necessarily mean that they are not biocompatible and safe. It only means that they have not been thoroughly tested and that nobody has applied for approval so far. Unfortunately, the market for airway stents is limited and companies are not enthusiastic to go through the long and costly process of getting these prostheses approved as long-time implants. The legal issues have been discussed elsewhere [31]. There is a widening gap between the technical opportunities using rapid prototyping techniques and the legal and administrative requirements for getting medical devices into the market. The presented technique could be a compromise to produce a perfectly matching stent within a couple of days for temporary use. It would have to be replaced during the following 28 days by a silicone molded stent that can be left in place much longer.

This approach would provide immediate relief for a suffering patient. It could also provide the opportunity to modify the later produced stent if needed. The biomechanical stent tissue interaction often requires replacing a stent anyway, e.g. if a dilatation effect has developed or a tumor has responded to therapy. There are many practical problems that need to be solved besides the materials. The stent design requires the cooperation between the treating physician and experts with engineering background. 3D printers and lasers are affordable, but it requires experience to master them. Even with the demonstrated rapid prototyping techniques, the stents must be sterilized, delivered to the hospital in time and inserted with feasible instruments. Therefore, this paper can only be a proof of concept and a stimulus for further research.

Conflicts of Interest (COI) Statements

None to declare.

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