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FABRICATION OF A 3D PRINTED EVEROLIMUS-ELUTING STENT MADE OF THERMOPLASTIC POLYURETHANE AND POLYLACTIDE

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Bronchial stenoses are one of the most common airways complications after lung transplantation. One of the main methods to restore airway patency is bronchial stenting. However, bronchial stenting is associated with a number of complications, such as stent migration, granulation tissue formation along the proximal and distal edges, and mucus obstruction of the lumen. This article demonstrates the possibility of manufacturing an everolimus-eluting stent from thermoplastic polyurethane and polylactide using 3D printing.

Keywords: lung transplantation, airways complications, bronchial stenosis, bronchial stenting, silicone stents, metal stents, bioresorbable stents, 3D printing, drug-eluting stents.

Bronchial stenosis is one of the most common airway complications occurring in lung transplant survivors. There is a definite pattern between the types of bronchial complications and the timing of their occurrence [1]. The most common time for stenosis occurrence is the first 2–9 months after lung transplantation [2]. Bronchial stenting is a generally accepted technique for restoring and preserving airway lumen with subsequent prevention of occurrence [3–8].

Based on fabrication material, there are usually two groups of stents used in interventional pulmonology: silicone and metallic stents [9]. Stents made of biodegradable materials should be singled out as a separate group.

There are several variations of silicone stents that differ in shape. The main types include T-tube tracheal stent [10], Dumon stent [11], Y-stents [12] (Fig. 1).

In turn, metallic stents used in endoscopic practice can be divided into self-expanding and balloon-expandable stents. In addition, stents are divided into covered and uncovered [13] (Fig. 2).

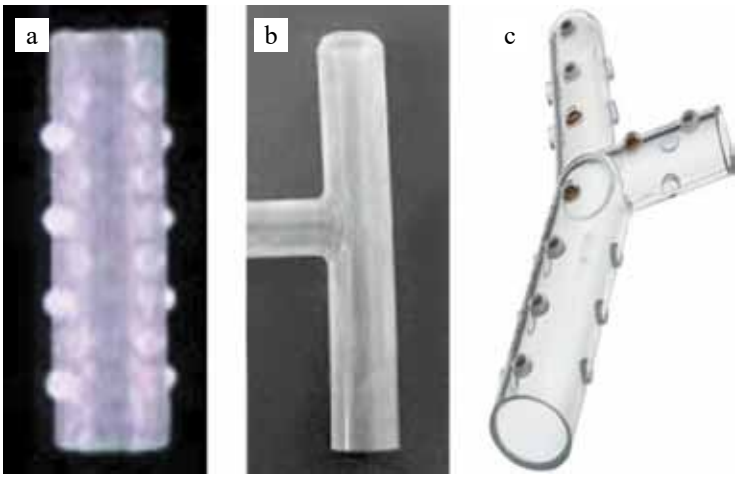

Fig. 1. Main types of silicone stents: a, Dumon stent; b, Montgomery stent; c, Oki Y-stent

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MAJOR COMPLICATIONS ASSOCIATED WITH TRACHEOBRONCHIAL TREE STENTING

Each of the stent options considered has both advantages and disadvantages that determine the choice of a particular stent in a specific clinical situation.

The main complications associated with having a stent in the lumen of the tracheobronchial tree include granulation tissue growth, stent migration, and sputum obturation.

Stent migration is more common when using Dumon silicone stents than when using Y-shaped silicone or metallic stents [12]. Migration can be caused by a mismatch between the size of the stent and the airway, including the mismatch between the stent and the anatomy of the tracheobronchial tree. Stents can migrate both proximally and distally. Proximal migration can cause acute severe respiratory failure (Fig. 3).

Distal stent migration can disrupt bronchial ventilation with the development of atelectasis and pneumonia.

Stent obstruction by bronchial secretion occurs as a result of stagnation of the content, which is normally removed from the bronchial lumen. Eventually, impaired evacuation of bronchial contents may lead to stent colonization [14]. As a rule, stent obstruction is most characteristic when using long silicone or covered nitinol stents, as well as stents with complex configuration (Montgomery stent, Y-stent).

The presence of stent in the lumen of the tracheobronchial tree causes local inflammatory response, leading to the growth of granulation tissues [15] (Fig. 4).

The inflammatory response is caused by local tissue hypoxia, which activates a cascade that releases chemokines and cytokines [16]. The end result is fibroblast activation and proliferation. Granulation tissue growth occurs predominantly along the proximal and distal edges.

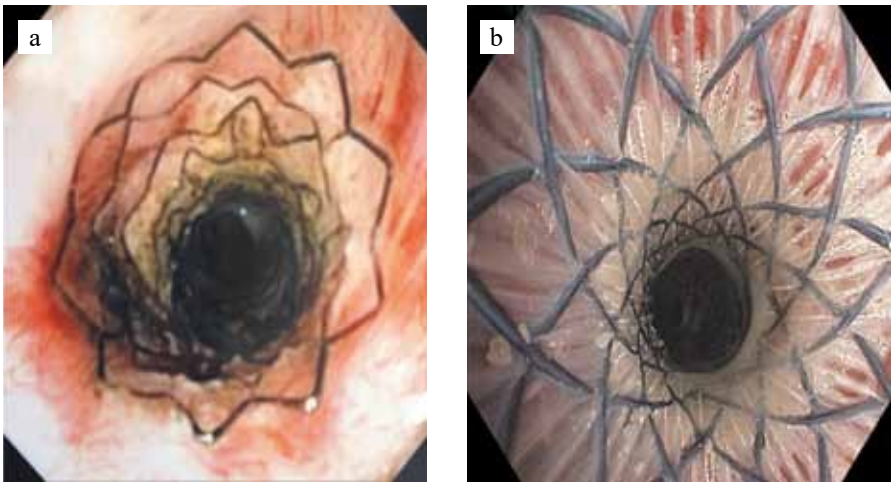

Fig. 2. Types of stents by coating: a, uncoated metallic stent; b, coated metallic stent

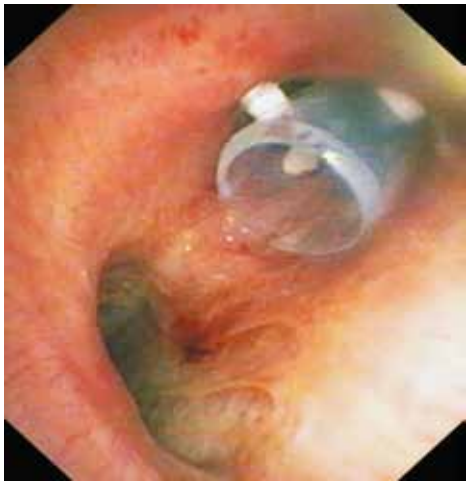

Fig. 3. Proximal migration of a stent placed in the intermediate bronchus, blocking the lumen of the right superior lobe bronchus

Uncovered metallic stents have a high rate of recurrent stenosis, including due to the sprouting of granulation tissue into the stent lumen [17]. When using covered metallic stents, the granulation tissue does not grow into the stent lumen.

BIODEGRADABLE STENTS

The use of biodegradable materials in stent fabrication should reduce tissue reactivity to foreign bodies in the airway lumen. Also, the ability of the stent to hydrolyze and its subsequent degradation may probably reduce the incidence of biofilm formation and stent colonization.

The timing of stent retention in the bronchial lumen is also a matter of debate. Many authors agree that the average time should be from 6 to 12 months, provided that there are no complications requiring stent retrieval or re-stenting [18–19]. However, Fonesca et al. reported

1 to 7 years as follow-up periods for lung recipients with stents [20]. Often, removing a stent from the airway lumen, especially for metallic stents, is connected with certain technical difficulties associated with the risk of breaking the stent frame during retrieval, which ultimately leads to bleeding and bronchial wall rupture. The use of biodegradable materials in stent fabrication makes it possible to avoid the stent removal procedure.

One of the main materials used in the creation of biodegradable stents is polydioxanone (PDS). This material retains mechanical strength for 6 weeks and completely hydrolyzes after 3–4 months [21].

In 2011, Lischke et al. used PDS stents in 6 lung recipients with central bronchial stenosis [22]. The stents made from PDS had a range of standard sizes, were uncovered and had a braided shape. Median stent diameter ranged from 8 to 17 mm and median length from 12 to 30 mm. A total of 12 implantations were performed. In 4 patients, re-stenting had to be resorted to due to recurrent stenosis. Median time to any re-stenting was 5 months. On average, the stent was completely degraded 4 months after implantation.

DRUG-ELUTING STENTS

The use of drug-eluting stents may be a way to potentially reduce the incidence of stenting-associated complications, as well as increase the therapeutic effect of this intervention.

As mentioned above, the growth of granulation tissues along the proximal and distal edges of stents that are implanted in the lumen of the tracheobronchial tree is primarily associated with local inflammatory response, the final link of which is fibroblast proliferation. A similar mechanism is encountered in cardiovascular surgery when stents are implanted in the coronary lumen. Drug-eluting stents have found wide application in endovascular interventions. The use of drugs that reduce fibroblast proliferation ultimately reduces the number of complications associated with coronary artery stenting [23–26].

Zhu et al. experimentally evaluated the effect of mitomycin-eluting stents on the development of tracheal stenosis in rabbits [25]. The stent material was a mixture of polylactide (PLA) and polycaprolactone (PCL). Implantation was performed through a tracheotomy with stent suturing. In order to enhance tracheal tissue damage and, as a consequence, fibroblast proliferation, thermal exposure via monopolar coagulation was used. For mitomycin-eluting stents, the incidence of stenosis was lower than in the control groups (tracheal damage without stent implantation and use of a silicone stent without drug coating).

Chao et al. implanted cisplatin-eluting PCL tracheal stents in rabbits [26]. The stents were implanted through tracheotomy. Follow-up was 5 weeks. After the indicated time, no signs of stenosis were revealed at autopsy. Histological study showed the presence of ciliated epithelium with minimal leukocytic infiltration of the submucosal layer where the stent was located.

One of the main problems arising in the use of drug-eluting stents is uncontrolled and, often, instant release of the drug. Lee et al. described a technique for polydopamine-mediated immobilization of various molecules on the surface of a PLA stent [27].

Jumat et al. evaluated the degree of saturation and release of everolimus using polydopamine [28]. PLA polymer was used as a material. Everolimus immobilization on the surface of the material was evaluated using electron microscopy. Thus, when an intermediate layer of polydopamine was used, the amount of everolimus on the surface was significantly higher. The rate of everolimus release in buffer solution at 37 °C was lower in polydopamine-coated samples.

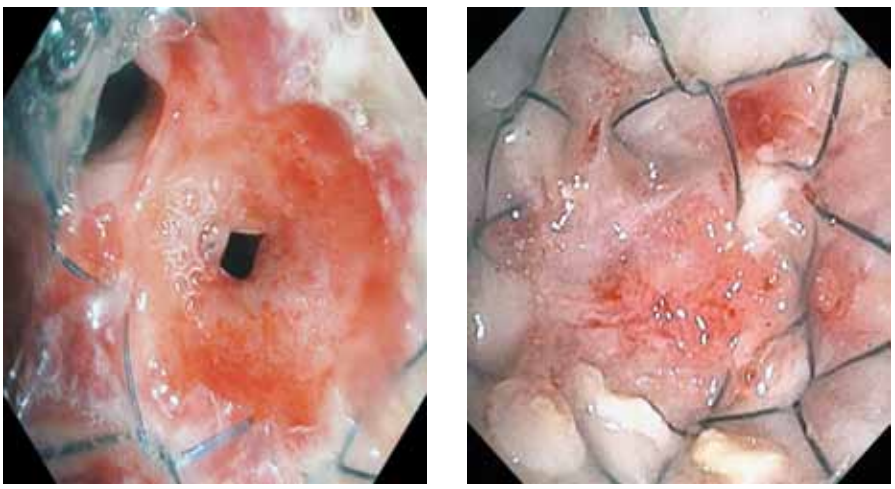

Fig. 4. Granulation tissue growth along the distal edge of the nitinol stent with stenosis formation

FABRICATION OF A 3D PRINTED DRUG-ELUTING STENT

Stents used in interventional pulmonology have standardized sizes and shapes. As a rule, each manufacturer has different stent options, differing in length and diameter. One of the main reasons causing stent migration is the mismatch between the anatomy of the tracheobronchial tree of a particular patient and the stent. In addition, stents with factory parameters do not take into account the localization of lobar and segmental bronchi, and the angle of departure.

Often, in order to adapt standard stents to the patient's anatomy, it is necessary to shorten the stent, create additional holes, and sew several prostheses [29]. These interventions lead to breach of design features, especially when using stents with weave.

Fig. 5. Stent model designed for subsequent printing

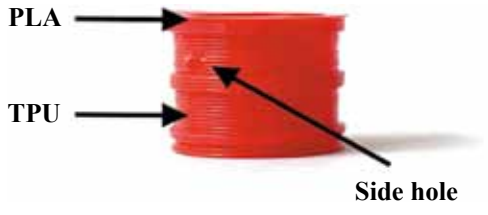

Fig. 6. Model of a 3D printed stent made by 3D printing (arrows indicate: PLA, polylactide rings; TPU, stent frame made of thermoplastic polyurethane; side hole, holes created on both sides of the stent in order to facilitate implantation)

Fig. 7. Left, stent before creation of polydopamine intermediate layer; right, stent with polydopamine intermediate layer

3D printing, also referred to as additive manufacturing, is a technology for manufacturing parts based on creating a physical object from an electronic model by adding material layer by layer. 3D printing of products has found wide application in medicine [30–31]. A model of the patient's tracheobronchial tree is created using CT scan data. Next, using modeling programs, a model of the stent is created with subsequent printing [32].

Fused deposition modeling (FDM) is a widely used additive manufacturing technique that creates three-dimensional objects through sequential, layer-by-layer application of plastic material. This technology has a number of advantages, including relatively low cost, a wide range of plastic materials, ability to print large objects, and availability of open source printers. It also allows for the creation of personalized models for each specific patient, which is critical to achieving the best possible treatment outcome.

Using a computer Aided Design (CAD) software solution, a 3D model of endotracheal stents was created, trying to combine the strengths of the most common stents in clinical practice (Fig. 5). The goal was to create a flexible stent similar to the Dumon stent, but with a strong framework capable of absorbing everolimus.

Thermoplastic polyurethane was chosen as the elastic base. The second plastic was polylactide, due to its high rigidity and hygroscopicity. After preparing the model for printing, a 3D printer that is capable of printing 2 different materials simultaneously was used.

Plastic filament was loaded into the printer and fed into the print head of the 3D printer. When exposed to the extruder, the plastic was extruded through the nozzle as a thin filament that was sequentially applied to the surface of the substrate. After each layer was applied, the plastic was cooled, causing it to solidify. This ensured the structural integrity of the layer before the next layer was applied. Gradually, layer by layer, the desired 3D object was formed (Fig. 6).

The fabrication of an everolimus-eluting stent was carried out with creation of an intermediate polydopamine layer. In order to polymerize dopamine, the stents were placed in the Tris-HCl buffer with pH 7.4. Also, dopamine hydrochloride was added to the solution at a ratio of 2 mg per 1 mL of buffer. Ammonium persulfate was used as a reaction catalyst and oxidant in a 1:2 ratio to dopamine hydrochloride [33]. Polymerization reaction was carried out at room temperature and in a dark room. After 24 hours, the color of the solution and stents changed to dark brown (Fig. 7).

The stents were washed in distilled water and placed in everolimus solution for 24 hours. Afterwards, the stents were removed and washed again in distilled water.

The microstructure of the samples was studied using field emission scanning electron microscopy (FE-SEM) on a Hitachi SU8000 electron microscope. Images were

captured in the mode of secondary electron registration at an accelerating voltage of 2 kV. Before imaging, the samples were placed on the surface of an aluminum table with a diameter of 25 mm, fixed with a conductive carbon tape and a conductive carbon layer with a 20 nm thickness was sprayed on it (Fig. 8).

CONCLUSION

Airway complications, particularly bronchial stenoses, reduce the quality of life and survival among lung recipients. The problem of airway complications is associated with the surgical aspects of transplantation, including the technique of procurement, organ preservation technique, bronchial anastomosis methods, the course of the postoperative period, including duration of ventilation, rejection episodes, occurrence of infections, immunosuppressive therapy regimen, and pathophysiological processes associated with bronchial wall ischemia.

It is worth noting that due to the high frequency of recurrences, there is no consensus on effective ways of correcting bronchial stenosis in lung recipients. One of the main lumen restoration methods is bronchial stenting.

The use of 3D printing makes it possible to create a stent that closely replicates the anatomy of the patient's airways. The materials used in 3D printing can be biodegradable.

Being an antiproliferative drug, everolimus can reduce fibroblast proliferation, thereby inhibiting granulation tissue growth. This property is actively used in endovascular surgery when creating drug-eluting coronary stents.

This article presents the experience of fabricating 3D-printed drug-eluting bronchial stents. Evaluation of the in vivo effect of these stents on experimental animals is the next stage of our research.

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The authors declare no conflict of interest.

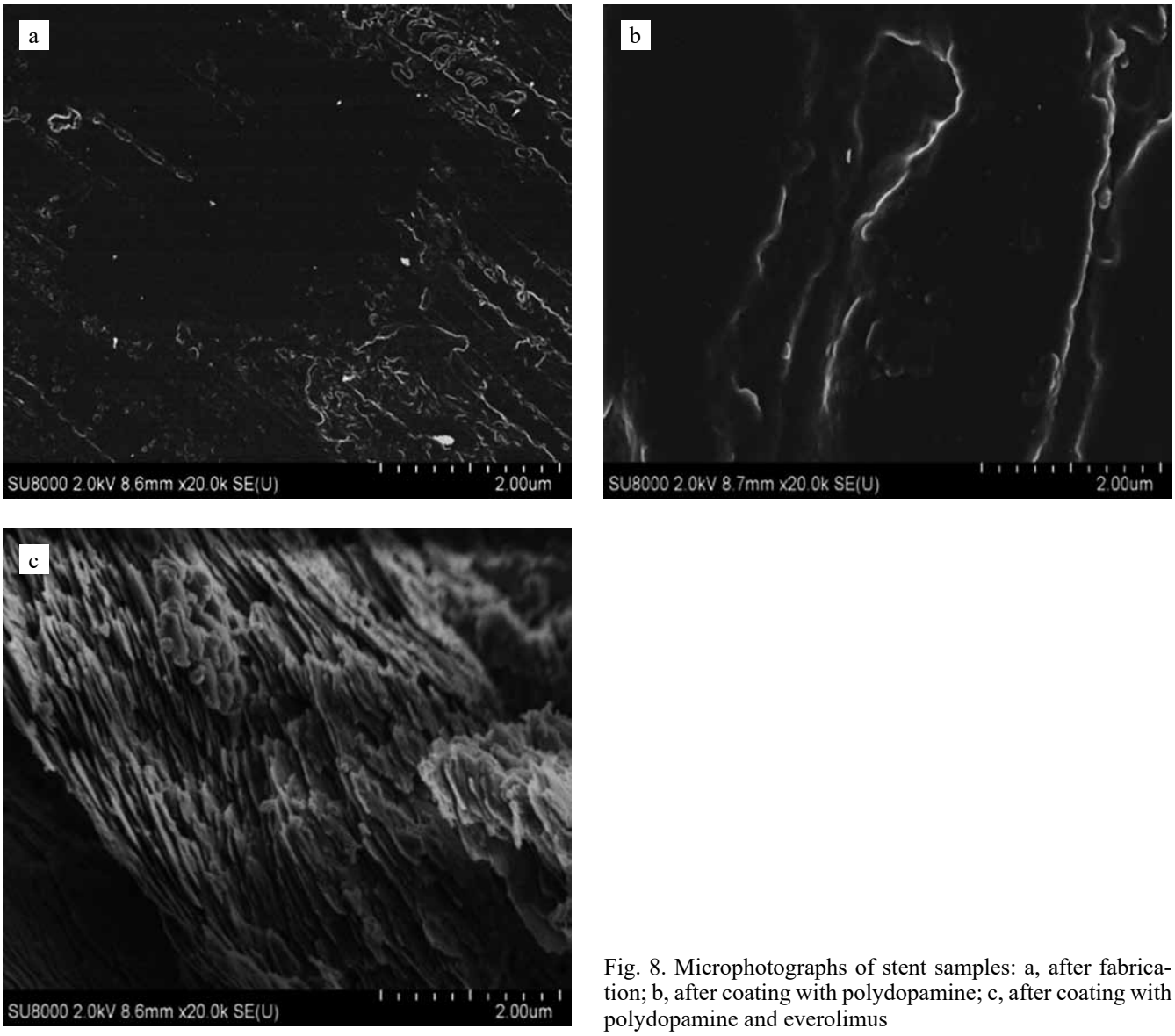

Fig. 8. Microphotographs of stent samples: a, after fabrication; b, after coating with polydopamine; c, after coating with polydopamine and everolimus

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