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Chapter

3D Printing and Airway Stents

Carlos Aravena and Thomas R. Gildea

Abstract

A central goal of an airway stent is to restore patency by preventing restenosis, holding the tracheobronchial wall, or occluding fistulas. Complications with stents, however, are frequent and can have grave repercussions. Stents are therefore viewed as a last resort in cases where other forms of treatment are ineffective. Furthermore, it is common for people with complex airways to have airway stents that do not fit them well, which can result in several complications. Three-dimensional printing technology was developed at the turn of the 20th century. It has been employed in a variety of applications and has transformed healthcare. This technology has mainly been employed in respiratory medicine to develop three-dimensional models of the airways and to make airway splints and prostheses to treat central airway diseases. In the past ten years, it has transformed and advanced personalized medicine, enabling the creation of patient-specific stents for people with complex airway diseases. Three-dimensional printing might be used to create a patient-specific stent that would lessen risks, enhance the quality of life, and eliminate the need for additional procedures. This chapter discusses the most recent developments in three-dimensional printing technology, how they are being used to create airway prostheses to treat complex airway illnesses and the current body of research that supports their use.

Keywords: three-dimensional printing, 3D-printing, bronchoscopy, airway stents, patient-specific airway stent, computer-aided design, three-dimensional airway mold, 3D airway mold

1. Introduction

A wide range of benign and malignant illnesses can impact the airway [1]. The diagnosis and treatment of these disorders rely significantly on bronchoscopy [2]. After non-invasive treatments are found to be ineffective, therapeutic bronchoscopy attempts to enhance the patient quality of life, reduce symptoms, and provide significant palliation [1, 3]. Flexible or rigid bronchoscopy (RB) is a procedure that can deliver a variety of therapeutic modalities, among them stent placement play an important role [1, 3–6]. Reestablishing patency, preventing restenosis, stabilizing the tracheobronchial wall, or occluding fistulas are the primary purposes of an airway prostheses [7, 8].

Stents could be made of metallic wire mesh, silicone, or a combination of these materials (hybrid), as well as various sizes and shapes [9]. It is typical to experience complications like migration, granulation, infection, and mucus clogging [7, 10–13].
Therefore, stents should only be temporary when no other methods can achieve appropriate and long-lasting patency [5, 14–16].

Because implantation may last long and result in a high rate of complications, using stents in benign obstructions require caution [14]. Due to the possibility of excessive complication rates uncovered metallic stents are not recommended for use in most benign airway diseases [14]. Silicone stents are the most popular choice for benign conditions [6, 14, 17]. The synthetic substance used to create silicone stents has a low tissue reactivity and is simple to remove [14, 16].

Unfortunately, there are not many sizes and forms of commercially available stents (CAS). Sometimes it’s crucial to modify them to enhance fit and performance, particularly in patients with complicated airway anatomy [18]. This Customization usually involves cutting and stitching stents together in the operating room and requires an expert and highly trained doctor [18].

Because of the intricate features of the tracheobronchial anatomy, Three-dimensional printing (3DP) technology is perfect for creating airway prostheses to treat difficult conditions. With the help of years of research and development, it is now possible to produce a patient-specific stent [19–22]. A patient-specific stent may help decrease risks, shorten healing time, and enhance patients’ quality of life while alleviating symptoms and avoiding the need for additional bronchoscopies.

Recent research has examined the use of 3DP technology to produce silicone and hybrid airway prostheses and investigate biodegradable materials and drug-eluting stents (DES) [23].

This chapter discusses the most recent developments in three-dimensional printing technology, how they are being used to create airway prostheses to treat complex airway problems, and the body of research that supports their use.

2. Airway diseases and three-dimensional printing

Anatomical modeling of various bodily components for preoperative planning purposes by surgeons was one of the earliest uses of rapid prototyping techniques in medicine [24, 25].

In respiratory medicine, 3DP technology has been used, particularly for conditions of the central airways. In 2013, Tam et al. printed inspiratory and expiratory three-dimensional (3D) models of the tracheobronchial tree of a patient with airway disease due to relapsing polychondritis, and they explored the potential use for surgical or interventional planning and teaching [26].

In a case study published in 2013, Zopf and colleagues described how a biodegradable airway splint was surgically inserted into a newborn’s malacic left main bronchus [27].

Then, in 2015, George Z. Cheng et al. published the first case study of a 3D-modeled T-tube inserted into a patient’s difficult upper airway. This prosthesis was made to allow for the three-dimensional reconstruction of the trachea from a computed tomography (CT) scan [28].

To treat a 56-year-old male patient with airway complications of granulomatosis with polyangiitis (GPA) who required numerous unsuccessful therapeutic bronchoscopies and multiple commercially and manually customized stents, Thomas R. Gildea created and implanted the first bronchial patient-specific airway stent (PSS) made of silicone under Food and Drug Administration clearance for compassionate use in 2016. He did this using CT imaging and 3DP technology [20, 22]. In 2017, Gildea and
colleagues described the one-year experience of this patient and another with complex airway disease attributable to GPA. Both patients improved their average time between treatments and stent life following implantation after inserting PSS made utilizing 3DP technology [20, 22].

Guibert et al. presented a case of a patient with an airway problem following lung transplantation in 2016; the right airway had dehiscence, a stenotic bronchus intermedius, and complex morphology. After a 3D airway was built from a CT scan, and the difficulties were virtually removed, a planned 3D mold was made and used to create a unique stent. It was successfully implanted with RB [29].

Similar efforts have been made in treating tracheobronchomalacia in adult patients using 3DP technology [29]. Shan and colleagues recently published their experiences with hybrid stents that were assisted with 3DP technology to treat malignant airway obstruction and aerodigestive fistula [30, 31].

3. Airway stents and 3D printing procedures

To make airway stents, many 3D techniques and materials have been employed. In order to create a 3D reconstruction of the trachea using a CT scan, Cheng and colleagues employed 3D slicer, a free, open-source, and multi-platform software application that is frequently used for medical, biomedical, and related imaging research. The virtual T-tube was created using Solidworks® (computer-aided design (CAD) software) then a 3D model was imported, matching his patient's virtual difficult upper airway. The silicone customized T-tube was created and put through the tracheostomy stoma under bronchoscopy supervision [19, 28].

Gildea and colleagues used specialized software created for orthopedic surgery to transfer the digital imaging from a CT scan (COS Inc., Cleveland, OH, USA). The airway is turned into a virtual 3D prototype. The ideal stent dimensions, including the area, diameter, angulation, branching, length, and wall thickness, were defined using this virtual model of each patient's anatomy. The doctor creates a virtual depiction based on clinical requirements by placing spheres in the 3D airway and adjusting their forms and sizes using the software tools. Using 3DP technology, a mold of the prescribed stent is created, and medical-grade silicone is then injected into this mold to create the stent (Figure 1). External studs are inserted after the stent has been finished, cleaned, and polished to produce a flat surface. The stent is sterilized using steam sterilization. The stent is then implanted utilizing RB and conventional procedures and instruments [20, 32].

Guibert employed a similar process, creating a virtual 3D mold (VGStudio MAX software). To create an Ertacetal POM mold, the 3DP (RolandDG MDX 40A) was fed with the 3D data. This mold was used to create a personalized silicone stent. The stent is placed during a therapeutic RB procedure [29, 33].

Using CAD software, Shan and associates could recreate 3D representations of the airway using information from a 64-slice multidetector spiral CT scan (Vitaworks, Shanghai, China). After different colors were given to the airway and tumor, the image was transformed into a 3D stereolithographic (STL) file. An airway mold composed of photosensitive polymers was produced using the 3D reconstruction data and a 3DP (RS600, Union Tech, Shanghai, China). The dimensions of the 3D-printed airway mold's area of interest were measured. The temperature-memory nickel-titanium alloy-covered self-expandable Y-shaped metallic airway stents (Micro-Tech, Nanjing, China) were then created utilizing the 3D printed airway model as a template.
Flexible bronchoscopy was used to evaluate the patient and install the guidewires before inserting the stents. A stent delivery system was advanced posteriorly out from the endotracheal tube, and the stent was deployed with fluoroscopy [30, 31].

4. Biodegradable stents

Research is being done on biodegradable stents (BDS) that might temporarily sustain patency in an airway [34]. They may be helpful when temporal stenting is desired in individuals with benign airway disorders [9]. The prosthetic material must be biocompatible, release harmless residues as it degrades, be strong enough to maintain the integrity of the airway, and be durable enough to allow the airway to reconstruct [34, 35]. Research has been done on several synthetic degradable polymers, including polyesters containing lactic acid, glycolic acid, dioxanone, caprolactone, polytrimethylene carbonates, polyanhydrides containing sebacic acid, and polycaprolactone generated from tyrosine [34, 36–38]. Studies in animal models showed that, depending on the polymer employed, stents had a high safety profile, were biocompatible, and degraded quickly over time [38–40].

According to studies conducted on patients, the BDS is safe and reduce symptoms. However, several patients might develop cough, mucosal hyperplasia, granulation tissue, biofilm, expectoration of stent parts after insertion, and other complications resulting from a lack of radiation force or re-stenosis [41–43].

Related to 3DP and BDS, research has been done on materials that can be directly printed to create an airway stent. In 2015, Nidah M. Hussain from the University of South Carolina used 3DP technology to design and print a bioresorbable tracheobronchial stent to investigate potential improvements on existing stents. He concluded that thermoplastic polyurethane is potentially viable as a biologically degradable silicone substitute and polycaprolactone is compatible with fused deposition modeling printing [44].
With the use of elastomeric polyurethane (EPU), Catherine Wood and colleagues created a platform for designing and manufacturing 3DP flexible airway EPU stents. They concluded that the 3D-printed EPU stent performs similarly to silicone stents after conducting comparison testing [45].

In an in-vivo examination of healthy rabbits, Paunovic et al. reported employing a digital light 3DP customized bioresorbable stent. The stents were made of biocompatible dual polymer that remained in situ for seven weeks [46].

Because of the potential for quick and direct manufacture, customization, biocompatibility, and degradability, these 3DP materials seem promising. However, more investigation should be done to enhance degradation time, radial force and reduce problems, particularly re-stenting before it is used in patients.

5. Drug eluting stents

DES have been widely used in cardiology to decrease coronary stent complications such as re-stenosis or stent thrombosis [47].

The use of stents in central airway obstruction has been related to numerous complications and looking to reduce adverse events (AEs) rate or to treat airway obstruction airway-DES research has been ongoing since the last decade [48].

In 2011, Zhu and colleagues randomized different types of stents in 20 rabbits, the bioabsorbable stents with mitomycin C had the best performance, with less mucus plugging and airway obstruction [48]. Other drugs have shown to decrease the granulation tissue or scar formation in animal models, such as airway DES with paclitaxel, sirolimus, methylprednisolone, or cisplatin [49–54].

The potential use of DES in airway diseases is not limited to preventing mucus plugging or granulation tissue formation. It could prevent stent-related infection, treat long-term malignant central airway, or manage benign central airway stenosis. Several chemotherapeutic, anti-proliferative, or antifibrotic agents have been proposed [55].

3DP technology can be used to create a personalized drug-eluting stent. According to the patient’s need, it could have different polymers and drugs or a combination to produce a sustained drug release effect and prevent or treat different conditions [56].

6. 3D printing and clinical research

The number of studies on 3DP and airway stents has grown since 2015. Ten publications using 3DP and PSS in humans were identified (Table 1) [22, 28–33, 57–59]. Most studies have focused on benign airway conditions such as tracheobronchomalacia, post-radiotherapy airway complications, post-surgical airway complications, post-transplant airway illnesses, and GPA airways. Silicone was the most used stent material in benign airway disorders [22, 29, 32, 33, 57, 60, 61]. Malignant central airway obstruction and malignant aerodigestive fistula have been the subjects of more recent research. Except for one study, they utilized covered metal stents [30, 30, 58].

To produce the PSS, nine studies reported printing a 3D airway mold (there is no description in one study). Additionally, Y tracheobronchial or bronchial stents were the majority. In six studies, Y-bronchial stents or a bronchial branch to the right upper lobe were made using a 3D mold.
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Type of study</th>
<th>N° patients</th>
<th>Type of airway disease</th>
<th>Airway mold</th>
<th>Stent shape</th>
<th>Stent material</th>
<th>Results</th>
<th>AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheng et al.</td>
<td>2015</td>
<td>Case report</td>
<td>1</td>
<td>Benign</td>
<td>Yes (virtual)</td>
<td>T-Tube</td>
<td>Silicone</td>
<td>Improvement in phonation, no granulation tissue after 4 months f/u</td>
<td>N/D</td>
</tr>
<tr>
<td>Guibert et al.</td>
<td>2017</td>
<td>Case report</td>
<td>1</td>
<td>Benign</td>
<td>Yes</td>
<td>Right bronchial stent branched to the RUL</td>
<td>Silicone</td>
<td>Improvement of symptoms, PEF</td>
<td>N/D</td>
</tr>
<tr>
<td>Gildea et al.</td>
<td>2018</td>
<td>Case report</td>
<td>2</td>
<td>Benign</td>
<td>Yes</td>
<td>Y-stent for LMB</td>
<td>Silicone</td>
<td>Increased time between procedures, Increase stent life, Decrease procedure time</td>
<td>N/D</td>
</tr>
<tr>
<td>Schweiger et al.</td>
<td>2018</td>
<td>Case report</td>
<td>2</td>
<td>Benign</td>
<td>Yes</td>
<td>Y Tracheobronchial</td>
<td>Silicone</td>
<td>Symptoms improvement</td>
<td>N/D</td>
</tr>
<tr>
<td>Guibert et al.</td>
<td>2019</td>
<td>Prospective</td>
<td>10</td>
<td>Benign</td>
<td>Yes</td>
<td>Y bronchial and tracheobronchial stent</td>
<td>Silicone</td>
<td>90% congruence, 80% improvement in dyspnea, quality of life and FEV1 or PEFR</td>
<td>Complication rate of 40% at 3 months f/u</td>
</tr>
<tr>
<td>Aravena Leon et al.</td>
<td>2019</td>
<td>Retrospective</td>
<td>4</td>
<td>Benign</td>
<td>Yes</td>
<td>Y bronchial and tracheobronchial stent</td>
<td>Silicone</td>
<td>No difference compared to commercial stents in RB loading, placement, removal, Increase time between procedures, Increase stent life</td>
<td>PSS had a lower severity of migration. All other AEs were not statistically different between the two groups.</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Type of study</td>
<td>N° patients</td>
<td>Type of airway disease</td>
<td>Airway mold</td>
<td>Stent shape</td>
<td>Stent material</td>
<td>Results</td>
<td>AEs</td>
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<tr>
<td>Duong et al.</td>
<td>2020</td>
<td>Case report</td>
<td>1</td>
<td>Malignant</td>
<td>N/D</td>
<td>Right bronchial stent branched to the RUL</td>
<td>Polyurethane</td>
<td>Symptoms improvement</td>
<td>PSS replacement at 2 months and migration and removal of the 2nd PSS</td>
</tr>
<tr>
<td>Huang et al.</td>
<td>2020</td>
<td>Retrospective</td>
<td>6</td>
<td>Benign (Post-esophagectomy)</td>
<td>Yes</td>
<td>Y Tracheobronchial</td>
<td>Hybrid (Nitinol, Silicone and PTFE)</td>
<td>All fistulas sealed. Leaking control in 6 patients. KPS improvement</td>
<td>2 patients had mucus retention, 1 had excessive granulation tissue and stent removal</td>
</tr>
<tr>
<td>Shan et al 2021</td>
<td>Retrospective</td>
<td>12</td>
<td>Malignant</td>
<td>Yes</td>
<td>Y stent (1 bronchial, rest tracheobronchial)</td>
<td>Hybrid (Nitinol, Silicone and PTFE)</td>
<td>1 patient had 2 stents. 11 had significant symptoms improvement, KPS improvement</td>
<td>4 patients had mucus retention, 2 excessive granulation tissue, 0 migration, 0 removal</td>
<td></td>
</tr>
<tr>
<td>Shan et al 2021</td>
<td>Retrospective</td>
<td>26</td>
<td>Malignant TEF and post-esophagectomy</td>
<td>Yes</td>
<td>Y stent (1 bronchial, rest tracheobronchial)</td>
<td>Hybrid (Nitinol, Silicone and PTFE)</td>
<td>Clinical success rate 80% Resolution TEF post-esophagectomy (9/16). Resolution malignant TEF (0/10). KPS improvement</td>
<td>2 (7.69%) patients had granulation tissue treated with cryotherapy and stent removal, 5 (19.23%) sputum retention, treated w/ suction. 1 (3.84%) had stent migration underwent a second stent. 1 (3.84%) not tolerate the stent and was removed.</td>
<td></td>
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Table 1. Clinical studies description of PSS assisted by 3DP technology.
Improvement in symptoms was observed in all studies (Table 1). Guibert et al. used 3DP silicone PSS in 10 patients, the majority had post-transplant airway complications and reported high rates of congruence between the stent and the airway, 80% improvement in dyspnea (>1 New York Health Association score point gain), quality of life (>10% increase in VQ11 Chronic Obstructive Pulmonary Disease-specific quality of life score), and pulmonary function test (>10% Forced Expiratory Volume in 1 second (FEV1) or Peak Expiratory Flow (PEF) increase) [33].

A retrospective analysis of patients who got 3DP silicone PSS at the Cleveland Clinic was reported by Aravena et al. Interventional pulmonologists completed a survey and two physicians rated stent-related AEs using the Common Terminology Criteria for Adverse Events scoring system. Four patients received a total of 13 PSS. No difference was noted in the loading, positioning, or removal of the PSS in comparison to the CAS (p > 0.05). Following the placement of the PSS, bronchoscopists saw a substantial clinical improvement (p = 0.03). The PSS’s average lifespan was considerably longer than the CAS’s (300.2 days vs. 124.0 days, p = 0.001) by a large margin. With PSS, the median time between bronchoscopies was significantly longer than with CAS (65.6 days vs. 36.6 days, p = 0.004) [57 , 61].

In a study by Shan et al., 12 individuals with malignant airway obstruction caused by lung or esophageal cancer had 13 covered metal PSS implants. Hugh-Jones dyspnea scale and Karnofsky performance status (KPS) improvements were reported (P = 0.003 and P = 0.006, respectively) [30].

Regarding the AEs that were portrayed in the different trials. At three months, Guibert and colleagues reported a 40% complication rate, one patient with a mucus plug, two stent migrations, and one untreatable cough. Three of them needed to have their stents removed. One patient experienced distal stenosis at a lobar level that needed balloon dilatation, and another mucus plug incident occurred at the end of the four-month follow-up period. There were no life-threatening problems found [33]. Aravena and associates found that silicone PSS had less severe migration than CAS (p = 0.0225). The statistical differences between the two groups did not exist for any other AEs [57 , 61]. Shan et al. demonstrated a 50% (6/12) complication rate with coated metal PSS after 5.6 months of follow-up. Only two patients had significant granulation tissue development, four patients had mucus blocking, and no patients needed their stents removed or had migration [30].

7. Discussion

Using any stent is always a last resort in cases of complex benign or malignant airway diseases. There are several problems associated with stents. Migration, stent obstruction by either granulation tissue or mucus, and infection are the three most frequent adverse outcomes of silicone stenting. These disorders can also be interrelated [5, 6, 14–18]. Even with non-malignant diseases, many patients still benefit from long-term palliation despite the risk.

The technical success of the PSS congruence to the complicated airway is high. It can result in a decline in AEs because fit issues could be responsible for many stent-related consequences. The migration rate is greater for either too loose or too tight stents. Excessive pressure from a stent on the airway might cause tissue necrosis and perforation. An improperly fitted stent may promote granulation at the ends or result in poor secretion clearance. Additionally, the material used may have clinical
implications. Even in silicone stents, there are prostheses with a different durometer and elastic modulus that can have a distinct impact on wall stress.

The benefits could be substantial. Through all the research mentioned, symptoms have consistently improved. In one study, the lung function test and quality of life improved [31]. The PSS and CAS were only contrasted in one research. This showed a longer stent life and longer intervals between treatments, which may be associated with an improvement in the quality of life for patients with complicated benign airway diseases who often need several consecutive bronchoscopies to try to achieve palliation [57, 61].

Improving performance status scale is an important additional finding related to malignant disorders [30, 31, 58]. It could be linked to decreased adverse events (AEs), better congruence, and airway obstruction relief, which would aid with symptoms and possibly enhance clinical performance, allowing for the potential of receiving oncologic therapy.

Additionally, the 3DP PSS is at least as secure as the CAS. The rate of complications is comparable, and no problems that threaten life have been reported. The development of 3DP PSS with Y-bronchial and Y-tracheobronchial stent shapes, which are compatible with and suit the intricate airways of those patients, likely contributed to a reduction in migration rate compared to CAS (Table 1) [57, 61].

The PSS may be loaded and inserted using traditional techniques, just like conventional stents [57, 61]. This is crucial since deploying some complex stent designs, such as the dynamic Y-stent, requires specialized equipment.

The research in 3DP PSS do not have a sufficient sample size to generalize the application of patient-specific stenting. Many studies are retrospective cohorts or cases, which are both highly biased. But the early experience has demonstrated that PSS are highly successful and safe in the palliative treatment of extraordinarily complicated airway diseases, above all currently available best practices, despite the small sample size.

8. Future directions

3DP technology is developing fast and will be an important tool for personalized medicine in patients with complex airway diseases. Research is still being done to make more advancements. New materials that might be directly printed and biodegradable may be preferred when temporal stents are needed [46]. Additionally, 3DP drug-eluting stents might be a feasible therapeutic strategy for avoiding excessive granulation tissue, precluding infections, and managing malignant or benign obstruction of the airway [23, 62].

We envision the future of 3DP of completely compatible or engineered biological tissue prosthesis that promotes improvement of the damaged tissue and replace part of the impaired airway.

9. Conclusion

Over the past few decades, 3DP technology has made significant progress. This technology has been applied to healthcare for preoperative planning, education, medical equipment, prostheses, implants, and medical models. Respiratory medicine is at the forefront of a revolution in personalized treatment by making individualized
Airway stents tailored to the unique requirements of patients with complicated malignant or benign airway disease. These patient-specific airway stents developed utilizing 3DP technology can potentially reduce the number of treatments needed and adverse events (AEs) and improve symptoms and quality of life.

To ascertain the real impact this technology will have on this group of patients, new research with markedly better methodology will be necessary yet challenging.

**Conflict of interest**

CA has no conflicts of interest to declare. Visionair is the manufacturer of one of the Stents created with 3DP technology presented in this review. TRG is the inventor and may be entitled to royalty payments from the company in accordance with Cleveland Clinic policy.

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