Biodegradable Airway Stents – Bench to Bedside: A Comprehensive Review

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Key Words

Airway stenting · Degradable biomaterials · Biodegradable stents · Animals · Humans

Abstract

Airway stents are indicated to treat symptomatic narrowing or to close fistulas of the central airways. They are generally divided into two types: the silicone stents and the metallic stents. Unlike in malignancies, removability is a major objective of temporary stenting in benign conditions, which poses the challenge of a new rigid bronchoscopic procedure under general anesthesia and stent removal with all its attendant risks and costs. The concept of a biodegradable (BD) stent that could maintain the patency of an airway for a predetermined duration of time is very appealing. These BD stents would gradually degrade and eventually vanish from the airway once they are no longer needed. Such stents are currently an area of intense research. Another very promising concept of drug delivery with such stents is also a very exciting area of current research. The aim of this comprehensive review is to discuss all pertinent available literature on the use of BD materials in various clinical applications and to extensively review all animal and humans trials involving BD airway stents.

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Introduction

The main purpose of a stent in the airways is to restore and maintain patency. Any endoluminal or extrinsic pathology causing more than 50% reduction in airway lumen and leading to debilitating symptoms such as dyspnea may be an indication for airway stents [1, 2]. Five major indications for airway stenting include [2]: extrinsic airway compression from tumors or lymph nodes, maintenance of airway patency after debulking of intraluminal benign or malignant obstruction, treatment of benign stenoses, stabilization of collapsing airways in conditions such as malacia, and treatment of fistulas (e.g. stump dehiscences or tracheoesophageal fistulas). Airway stents are generally divided into two types: the silicone stents and the metallic stents [2, 3].

In malignant conditions, both silicone and metallic stents show a similar efficacy and safety profile [4–6] due to a short life expectancy despite the lack of a randomized study comparing the two kinds of stents. Patients usually expire prior to any discernable difference in terms of long-term complications related to different types of stents being detected. In addition, in malignant conditions, palliation is often the objective, and removability of the stent is generally not a concern due to the short sur-

vival of the patient. Exceptions to the above are treatment-naïve patients with malignant central airway obstruction who underwent stenting for relief of dyspnea. Small-cell-carcinoma patients who received chemotherapy and non-small-cell-carcinoma patients who underwent radiotherapy can often demonstrate a reduction in the tumor size thus eliminating the need for long-term stenting. Treating benign lesions with airway stents requires particular attention to issues such as long-term complications and removability [2]. In general, only removable stents should be used for these indications until a multidisciplinary team has considered and exhausted [2, 3, 7] all other options including surgical repair. Even though airway stenting is generally considered as a palliative treatment, some studies suggest that it can be curative in and of itself. Benign posttracheostomy or postintubation tracheal stenosis can be successfully treated with silicone stents if held in place for 18 months in about 70% of the cases [8]. Similarly, anastomotic strictures after lung transplantation can also be treated with silicone stents with the same percentage of success when the stent is placed for a duration of 9 months [9]. Thus removability is a major objective of temporary stenting in benign disease, which poses the challenge of a new rigid bronchoscopic procedure under general anesthesia and stent removal with all its attendant risks and costs. The concept of a biodegradable (BD) stent that could maintain the patency of an airway for a predetermined duration of time is very appealing. These BD stents would gradually degrade and eventually vanish from the airway once they are no longer needed. Such stents are currently an area of intense research. Another very promising concept of drug delivery with such stents is also a very exciting area of current research.

The aim of this comprehensive review is to discuss all pertinent available literature on BD materials and their use in various clinical applications. We will also extensively review all animal and humans trials involving BD airway stents in this review article.

Existing BD Materials

Degradable materials must fulfill more stringent criteria in terms of their biocompatibility than nondegradable materials. In addition to the potential problem of toxic contaminants leaching from the implant, one must also consider the potential toxicity caused by the degradation products and subsequent metabolites [10]. Over the last decade, a number of hydrolytically unstable polymers have been suggested as degradable biomaterials. However, in most cases, no attempts have been made to develop

these new materials for specific medical applications. In addition, only a small fraction of these polymers have been studied in terms of their in vivo toxicological profiles, degradation rates and mechanisms, and their physico-mechanical properties [10]. An even smaller number of synthetic, degradable polymers have been used in medical implants and devices that have gained approval by the United States Food and Drug Administration (FDA) for use in patients. The FDA does not approve polymers or materials per se, but only specific medical devices and drug delivery formulations. As of 2006, only seven distinct synthetic, degradable polymer classes have been approved for use in a narrow range of clinical applications [11]. These polymers are polyesters containing lactic acid (poly-L-lactic acid, PLLA), polyesters containing glycolic acid (poly-L-glycolic acid, PLGA), polyesters containing dioxanone (polydioxanone, PDS), polyesters containing caprolactone (polycaprolactone, PCL), poly(trimethylene carbonates), polyanhydrides containing sebacic acid, and tyrosine-derived polyarylates. Various other synthetic, degradable biomaterials currently in clinical use are blends or copolymers of these base materials such as a wide range of copolymers of lactic and glycolic acid.

Mechanisms of Degradation and in vitro Testing of Biomaterials Used for Stents

The term 'degradation' refers to a chemical process resulting in the cleavage of covalent bonds. Hydrolysis is the most common chemical process by which polymers degrade but degradation can also occur via oxidative, photodegradative, and enzymatic mechanisms [10]. All polymers undergo some degree of degradation. Göpferich [12] defined 'degradable polymers' as those that degrade within the time scales of their expected service life or shortly thereafter. Conversely, 'nondegradable' polymers have degradation times that are substantially longer than their service life. Currently, at least four different terms (biodegradation, bioerosion, bioabsorption, and bioresorption) are used to indicate that a given material or device will eventually disappear after having been introduced into a living organism. The terms 'bioresorption' and 'bioabsorption' are used interchangeably and often imply that the polymer or its degradation products are removed by cellular activity (e.g., phagocytosis) in a biological environment.

Fibers made of PLLA, PDS, and polyglycolide-co- ϵ -caprolactone (PGACL) combine a relatively high initial strength and modulus together with sufficient ductility

and flexibility, and are therefore often chosen for use in stents [13]. In vitro, the effect of degradation on the tensile mechanical properties and morphology of these fibers has been examined. The expandable stents developed from these fibers demonstrate excellent initial radial compression strength. The PLLA stents exhibited excellent in vitro degradation resistance and can therefore support body conduits such as blood vessels for prolonged periods of time. PDS and PGACL stents can afford good support for 5 and 2 weeks, respectively, and can therefore be utilized for short-term applications. The degradation resistance of the stents correlates with the profile of mechanical property deterioration of the corresponding bioresorbable fibers.

Research and Medical Applications of Degradable Biomaterials

Five main kinds of degradable implants are possible:

- 1 A temporary support device is used when the natural tissue bed has been weakened by a disease, injury or as a result of surgery and requires some artificial support. The degradable implant would provide temporary, mechanical support until the natural tissue heals and regains its strength. In order for a temporary support device to work properly, a gradual stress transfer should occur: as the natural tissue heals, the degradable implant should gradually weaken. The need to adjust the degradation rate of the temporary support device to the healing of the surrounding tissue represents one of the major challenges in the design of such devices. Sutures for a healing wound or fixation devices for a broken bone [14] would be examples of the corresponding support devices. Tubular degradable stents have been manufactured for the treatment including various vascular (mainly coronary diseases) [15–23] and esophageal or bile duct [24–28] conditions as well as urethral [29, 30] strictures and have already been tested in animals and humans.
- 2 A temporary barrier has its major medical use in the prevention of postsurgical adhesions. During surgical closure, barrier devices are interposed between tissues that must remain separate following surgery.
- 3 Implantable drug delivery devices and injectable polymer-drug-depot delivery systems are capable of delivering drugs to specific locations over an extended period of time. They are, by necessity, temporary devices, for the drug reservoir will eventually be depleted or the need for delivery of a specific drug will be eliminated

once the disease has been adequately treated. The development of implantable drug delivery systems is probably the most widely investigated application of degradable polymers [31].

- 4 The tissue-engineering scaffold is a degradable implant that is designed to act as an artificial extracellular matrix by providing space for cells to grow into and be reorganized into functional tissue [32–34].
- 5 Multifunctional devices combine several of the above-mentioned functions within a single device [35–37]. Vascular and coronary stents are designed to mechanically prevent the collapse and restenosis of arteries that have been opened by balloon angioplasty and can deliver drugs (anti-inflammatory or anti-thrombogenic agent) directly to the site of vascular injury [38–41]. Drug-eluting/BD stents have also been studied in gastrointestinal diseases [42]. In vitro and animal studies have been conducted as well with BD tracheal stents either coated with dexamethasone [43, 44], cisplatin [45], or with mitomycin C (MMC) [46]. Zilberman et al. [43, 44] incorporated dexamethasone in a PLLA stent and showed that the cumulative release of dexamethasone from the stents was linear. Drug incorporation had a minor effect on the initial stent strength. Chao et al. [45] studied a degradable stent made of PCL coated with polylactide-polyglycolide copolymer and cisplatin. Kong et al. [47] studied, in vitro, the PLGA tracheal stent loaded with paclitaxel and demonstrated a favorable surface morphology as well as sustained and effective drug release behavior.

Airway Stenting with Degradable Biomaterials

Extraluminal splinting or scaffolding of the central airway with BD materials has also been studied in animals [48–57] and in two case reports in humans [58, 59]. The main objectives of these procedures were to stabilize a collapsing airway or to assist airway healing or remodeling after tracheal injury or surgery. Biomaterials used were diverse: copolymers of PLLA and PLGA [48–50], a copolymer derived from a dextran sulfate gelatin [51], a 3-layer scaffold consisting of a collagen sheet, a PLGA mesh, and a copolymer (L-lactide/ ϵ -caprolactone) coarse mesh [52], a copolymer of L-lactide and ϵ -caprolactone sponge tube reinforced by PLGA [53, 54], a polypropylene mesh tube with reinforcing rings with collagen extracted from porcine skin was conjugated to this frame and the luminal surface coated with a polymer, poly(L-lactic acid-co- ϵ -caprolactone) [55], a 3-dimensionally printed, bioresorb-

Table 1. Animal studies

First author [Ref.], year	Stented animals (n)	Material	Stent design	Technique of insertion	Degradation time
Chao [45], 2013	Rabbits (15)	PCL coated with PLLA-PLGA	Mesh-type stent made of interconnected ring-ellipse-ring units	Surgery	NS
Novotny [67], 2012	Rabbits (25)	PDS	Tubular and hollowed braided stent	Endoscopy + fluoroscopic guidance	2.5 months
Zhu [46], 2011	Rabbits (15)	PLLA-PCL	Helical stent	Surgery	NS
Liu [66], 2011	Rabbits (6)	PCL	Mesh-type stent made of interconnected ring-ellipse-ring units	Surgery	>8 months
Saito [65], 2004	Dogs (6)	PLLA	Knitted and hollowed tubular stent	Endoscopy	NS
Saito [64], 2002	Rabbits (15)	PLLA	Knitted and hollowed tubular stent	Surgery	14 months
Robey [63], 2000	Rabbits (25)	PLGA	Helical stent	Surgery	3.5 months
Korpela [61], 1999	Rabbits (11)	PLLA	Helical stent	Surgery	NS
Korpela [62], 1998	Rabbits (9)	PLLA	Helical stent	Surgery	NS
Lochbihler [60], 1997	Rats (35)	Vicryl	Homogeneous knitted stent	Surgery	2.5 months

NS = PCL: polycaprolactone, PLLA: poly-L-lactic acid, PLGA: poly-L-glycolic acid, PDS: polydioxanone.

able airway splint made of PCL [56, 59], and an external stent made of magnesium-yttrium alloy [57].

Animal Studies

Ten animal studies [45, 46, 60–67] regarding BD endoluminal airway stents have been published (table 1). The first study was performed in 35 rats by Lochbihler et al. [60] using stents made of vicryl filaments, surgically implanted in the trachea through a cervical median incision. Absorption time and compatibility were investigated. After 2 months no stent residues could be detected, whereas only signs of mild, chronic fibrotic inflammation persisted. No evidence for aspirations of foreign bodies or progressive inflammatory changes of the mediastinum was found.

Korpela et al. [61] experimented with self-reinforced PLLA helical stents in 18 rabbits and compared the local tracheal mucosal reaction to silicone stents; both stents were surgically implanted. PLLA stents were very well tolerated and caused only minor tissue reactions. Scanning electron-microscopic studies showed the ciliated cell layer was well spared between the spirals of the stent. The same authors [62] conducted another experiment in 32 rabbits and compared three types of stents (PLLA, silicone, and uncovered metallic stents). Their conclusions were that silicone stents had a tendency to occlude while stents made of metal and of self-reinforced PLLA were well tolerated.

Robey et al. [63] studied in vitro, mechanical and degradative properties of PLGA helical stents. Significant

mass loss was noted in vitro until after 5 weeks in buffer solution. By 14 weeks, the stents were nearly 100% degraded. The stents were then studied in vivo in a group of rabbits (12 were stented and 13 served as controls) who underwent anterior patch tracheoplasties. The stridor rate for the control group was higher than the stented group (38 vs. 17%) and a significantly higher average stenosis (34 vs. 23%) across the entire reconstruction site.

Saito et al. [64] surgically inserted PLLA stents in 15 rabbits and silicone stents in 8 rabbits. Biocompatibility and mechanical strength were studied. Good biocompatibility of PLLA stents was noted. The mechanical strength of silicone stents was greater than that of PLLA stents. The mechanical strength of PLLA stents increased as a function of their diameter. Degradation time was estimated at 14 months.

The first experimental study using endoscopic placement of degradable stents was conducted by Saito et al. [65] in 6 dogs. The objective was to assess the placement feasibility of a knitted tubular PLLA stent. The delivery system consisted of a flexible balloon catheter preloaded with a stent which was advanced to a target point in the trachea under bronchoscopic guidance. Once the stent was positioned, the balloon was inflated for 60 s. All stents were successfully placed with full contact with the tracheal wall.

PCL-made stents were for the first time studied in 6 rabbits by Liu et al. [66]. Safety and biocompatibility were investigated and were found to be good by the authors. Degradation time was estimated to be more than 33

months. PCL could be a promising bioresorbable material for stent design if prolonged degradation time is required.

Zhu et al. [46] investigated the effects and efficacy of a novel bioabsorbable tracheal stent made of a copolymer of PLLA and PCL with different designs (helical or tubular) in the rabbit model. They tested it with and without MMC elution for the prevention of diathermic-induced tracheal stenosis and compared it to silicone stents. All stents were surgically implanted. Tubular stents + MMC performed best. Tracheal stenosis was most significant for the helical stents, the control group, the group with tubular stents, and then the group with silicone stents. After 12 weeks, tracheal stenosis for the tubular stents + MMC was only half that of the silicone stents.

The first animal study using PDS as bioresorbable material was conducted by Novotny et al. [67] in rabbits. Stents were implanted bronchoscopically and under fluoroscopic guidance. The objectives were to study the biocompatibility of the stents using histological examinations and the degradation time. This latter was 10 weeks and the authors found an acceptable safety and biocompatibility.

Finally, Chao et al. [45] investigated the in vitro mechanical strength of a new cisplatin-eluting bioabsorbable stent made of PLLA-PLGA copolymer. Subsequently, the stents were surgically implanted in tracheas of the rabbits to study the in vivo cisplatin release. In vitro, mechanical strength was found comparable to the strength of a self-expandable metallic stent, and steady release of cisplatin for 4 weeks was observed. The in vivo study showed sustained cisplatin levels in rabbit trachea for 5 weeks. Degradation time of the stents was not calculated.

Human Studies

The literature regarding airway BD stents in humans is scarce. Lischke et al. [68] conducted a pilot study in order to evaluate the safety and efficacy of BD stents made of PDS (Ella-Cs, Ltd., Hradec Králové, Czech Republic) (fig. 1) to treat bronchial anastomotic stenosis in patients after lung transplantation. Twenty stents were implanted endoscopically in 6 patients presenting with posttransplant bronchial anastomotic stenoses (fig. 2). The endoscopic procedures included balloon dilation of the bronchial narrowing followed by the placement of the PDS self-expandable stent. The median stent diameter was 12 mm (8–17 mm) and median length was 20 mm (12–30 mm). All patients were evaluated clinically by bronchoscopy and high-definition computed tomography. All stents were placed successfully and relieved the steno-

Fig. 1. PDS stent placed in the left main stem bronchus stenosis.

sis in all cases. No complication was noted during stent placement. Four patients needed multiple stenting for anastomotic restenosis. Median time to any restenting was 5 months (2–15 months). One patient died from a pulmonary embolus and the remaining 5 were found to be in good clinical condition for up to 4 years (median 40 months, range 7–48 months) since first stenting and intervention free for up to 44 months (median 24 months, range 7–44 months).

Vondrys et al. [69] reported their experience with BD PDS stents for tracheal narrowing in children. Eleven custom-made PDS stents were implanted in 4 patients with airway narrowing due to external compression or intrinsic collapse. The median stent diameter was 9 mm (6–14 mm) and the median length was 15 mm (13–70 mm). Narrowing was initially relieved in all cases. There was no bleeding or perforation after stent implantation. Size mismatching was a problem in 2 cases. Three patients needed repeated stenting after stent absorption. There was 1 death, unrelated to the stent implantation. All 3 survivors were found to be in good clinical condition for up to 12 months after first stenting.

In a retrospective study, Serio et al. [70] described their experience of airway stenting in the management of tracheobronchial obstruction in children. During a period of 7 years, 235 stents were placed in 100 children. One

Table 2. Human studies

First author [Ref.], year	BD material	Patients/stents	Indications
Lischke [68], 2011	PDS	6 adults/20 stents	Anastomotic stenosis after lung transplantation
Vondrys [69], 2011	PDS	4 children/11 stents	External compression or intrinsic collapse
Serio [70], 2014	PDS	3 children/3 stents	(1) Tracheal stenosis after tracheostomy (2) Left main stem bronchus malacia (3) Tracheal stenosis
Antón-Pacheco [71], 2014	PDS	1 child/1 stent	Postoperative tracheal stenosis

tients and physicians when these devices are left in place for a long period of time [2]. These situations are almost exclusively encountered in cases of benign conditions when complications have time to occur, unlike in malignancies, where the majority of patients have limited survival. In the case of benign and symptomatic central airway narrowing, metallic stents that are not fully covered should be excluded from the physician's list of options because their removal can be very difficult and expose the patients to severe potential complications [2, 7]. Silicone and fully covered stents are the only acceptable options due to their relatively easy removability [3]. Previous studies have shown that after stent removal, conditions such as postintubation or posttracheostomy tracheal stenosis [8] and postlung transplantation anastomotic bronchial strictures [9] can be stabilized for a prolonged period of time in about 70% of the cases. In these studies, silicone stents were left in place for a mean duration of 9–18 months. These time periods suggest a potential benchmark for the longevity of the BD stents.

Animal studies show that the degradation time for the degradable biomaterial can vary from 8 weeks (Vicryl) to 14 months (PLLA). PDS and PLGA have a shorter degradation time (10 and 14 weeks, respectively) while PCL seems to have a significantly longer degradation time (>33 weeks). The time of absorption of a degradable stent can be modified depending on the choice of the basic molecule with which it is manufactured, the shape, the degree of polymerization, the internal arrangement of the material components, and the site of implantation [60]. Saito et al. [64, 65] reported that PLLA stents begin to degrade in 5–6 months while the total degradation time of PLLA is more than 1 year. Degradation time can be changed if the properties of the polymer such as the molecular weight, the size of the wire, and the shape are modified. The total degradation time of PLLA wire used in their study is predicted as 14 months, which is close to the

mean duration to treat benign tracheal stenosis in humans.

Only 4 papers report the use of BD stents in humans (table 2). The total number of patients in these papers is only 14, and the number of stents placed is 35.

In the pediatric literature, there are only 3 papers on this subject. In all the cases, stents were made of PDS. Endoscopic placement of these self-expandable stents seemed safe and user friendly in pediatric patients but failed to maintain airway patency in 2 patients [69] requiring their immediate removal. In the 12 remaining patients, the stents relieved the airway narrowing in the short-term but recurrences occurred in all the cases after stent degradation after 4–5 months of initial stenting. Of the 12 patients, 11 patients needed repeated BD stent placements and 1 was treated with a metallic stent.

In general, based on the data discussed earlier, degradation times seem longer in humans (4–5 months) compared to animals (2.5 months) [66].

There is no comparative study but it seems that the radial force of the Ella stent is lower than for self-expandable metallic or silicone stents. Only uncovered stents are available so they are not convenient for malignant conditions or fistulas. Their costs are higher than for other stents (above EUR 1,000).

At this time, neither PLLA, which seems promising in terms of degradation time, nor the combination of a BD and active stent has been attempted in humans. This seems surprising in comparison with other medical specialties such as cardiology in which stents made of different BD materials have been successfully tested in coronary artery diseases. In a recent review [23] the majority of the published studies have tested PLLA or PLGA BD stents activated with anti-proliferative agents and non-polymeric BD stents such as stents made of magnesium [28]. BD stents have been largely investigated in humans for the treatment of diverse gastrointestinal diseases. The

vast majority of these stents used PDS as the BD material [28]. PDX stents seem to be an attractive alternative to repeated dilations or surgery in patients with benign stenoses of the esophagus and of the small and large intestines. PDX stents have shown promising results but some aspects of this material/these stents need further improvement such as the loss of radial force over time due to the degradable material, which can induce mucosal or parenchymal injuries [28]. These issues in addition to a modest clinical efficacy have allowed limited indications of BD stents in gastroenterology [28].

In conclusion, benign, symptomatic, central airway diseases may require stents that must serve a temporary rather than a permanent purpose. Additionally, the use of BD stents could circumvent the long-term complications of permanent stents. However, BD implants are not without safety concerns, such as the toxicity of their degradation products and the degradation-related, premature failure of the implant. A large proportion of the currently investigated synthetic and degradable polymers are polyesters. It remains to be seen whether some of the alternative backbone structures such as polyanhydrides, polyphosphazenes, polyphosphonates, polyphosphoesters, polyamides [72], polycarbonates or magnesium will be able to compete with the well-established and well-stud-

ied position of the polyesters in the future. Manufacturers of BD stents will have to proceed to mechanical and physical research to adapt the design, the degradation time and the mechanical properties of their devices in order to withstand various environments such as airways. Stent size, shape, and mass are probably equally important for their biomechanical and degradation behavior. Hypothetically, a stent designed like a full tube of BD material will probably have a longer degradation time than a hollowed stent made with the same BD material. Ideal indications for BD stents in human airways have yet to be defined. Prospective studies are desperately needed in this area to answer the fundamental questions mentioned above and to determine whether there is a potential role of these stents in the rapidly widening horizon of the therapeutic bronchoscopies. With the advent of BD, active, and 3-dimensionally printed stents, the science of airway stenting has entered into a very promising phase of evolution. This evolution is particularly relevant in the era of personalized medicine.

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The authors have no conflicts of interest to reveal.

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