Study objectives: To assess the usefulness of an animal model for testing new tracheobronchial stents.

Setting: Animal laboratory of a university hospital.

Animals and interventions: In a series with 12 mini-pigs, we induced a stable fibromalacic tracheal stenosis that was 50% to 70% of the normal tracheal diameter. After dilation we inserted a 16 × 40-mm self-expandable silicone stent into the stenotic part of the trachea in 10 of the mini-pigs. Five of the stents had a smooth outer surface, and five had additional silicone retaining spikes. Because of a long stenosis in two of the mini-pigs, two overlapping stents (one smooth and one with spikes) were inserted.

Measurements and results: Stent deployment was successful and resulted in the disappearance of the slight to moderate stridor in all of the mini-pigs. Over a mean (± SD) observation period of 24 days (range, 10 to 41 days), all of the mini-pigs redeveloped stridor. Three of them died unexpectedly of suffocation: in all three a smooth stent had migrated, leading to total obstruction of the stenosis. In total, five of the six smooth stents migrated, and only one of the six spiked stents migrated. There was considerable granulation tissue formation at the ends of all of the stents. In the two control mini-pigs, a 12 × 35-mm Dumon stent was inserted. Both Dumon stents migrated, and one of them had considerable granuloma formation at its ends. At the end of the observation period, all stents were removed endoscopically and were found not to have deteriorated over time.

Conclusions: Our model proved to be suitable for the evaluation of the technical aspects of the Polyflex stent. Spikes on the outer stent surface are more effective in preventing migration than smooth-surface stents. Long-term compatibility, however, seems to be difficult to test with our model because both the Polyflex and the Dumon stents had excessive granulation tissue formation at both ends, a factor which—in the case of the Dumon stent—does not occur to such a degree in benign human airway stenoses. Our results indicate a need for prospective long-term studies in benign human airway stenoses.

Key words: animal model, central airway obstruction, stents, tracheal stenosis

Over the last decade there has been tremendous progress in the treatment of central airway obstruction, which is most often a result of malignant disease, and is attributed less frequently to benign disease. For endoluminal obstructions, such as a visible tumor within the airway, an array of therapeutic options exist, many of which are complementary. For obstructions in which the main component is extraluminal or extrinsic compression, the only endoscopic treatment modality apart from short-term dilation with a rigid bronchoscope is the placement of stents or endoprostheses.1 Many different stent models have been proposed for use in the tracheobronchial tree; the silicone stent designed by Dumon (Novatech; Aubagne, France) is the most widely used type.2–4 This stent is a cylindrical tube with regularly arranged studs on its outer surface that serve to anchor the device in the airway wall.

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Apart from the various silicone stents, expandable metal stents have also been used widely. Although most of them were developed for vascular use, insertion in the tracheobronchial tree proved to be quite successful from a technical point of view.\(^5\)–\(^7\) These stents consist of various forms of more or less densely woven wire struts or meshes, and are usually inserted under fluoroscopic control. Although they provide excellent initial palliation, their long-term results are often disappointing. Theoretically, these stents are epithelialized and therefore should be well tolerated. In reality they often lead to complications. In cases of malignant disease, tumor ingrowth through the wire mesh often occludes the stent as early as 2 to 3 months after placement.\(^8\) In benign disease the same problem arises through excessive granulation tissue formation. Furthermore, all of these stents are more difficult to remove than the Dumon stent. Many institutions therefore have abandoned the use of uncovered metal stents. However, metal stents have clear advantages: a very favorable ratio between the inner diameter and wall thickness, excellent adaptability to varying airway diameters, and the near absence of kinking. A current development is a metal stent covered with a thin layer of synthetic material that should prevent stent reocclusion. An example of such a device is the new covered Wallstent (Airway Wallstent; Schneider Europe AG; Bühlach, Switzerland), which has recently been commercialized in Europe.\(^9\)–\(^10\) The latest development in self-expandable airway stents is the Polyflex (Willy Ritsch AG; Kernen, Germany), which consists of a polyester wire mesh embedded in a silicone covering.

Before using newly developed stents in humans it would be helpful to test them in animal models. Marquette et al\(^{11}\) have recently described a model of tracheal stenosis in pigs that could be used for this purpose. We undertook the current study with a threefold purpose: we first wanted to validate the model of Marquette et al\(^{11}\) for the establishment of a stable tracheal stenosis. We then tested two different prototypes of the Polyflex stent: one has an almost smooth outer surface, and one has additional spikes on the outside. We hypothesized that the version with spikes would be superior to the smooth one in preventing stent migration. Finally, long-term tissue compatibility of the Polyflex stent was analyzed in comparison to the Dumon stent.

**Materials and Methods**

**Animals**

We used a series of almost fully grown mini-pigs (Göttingen Veterinary Faculty; University of Zurich, Switzerland); all were 18 months of age with a mean weight of 35.5 kg. They were kept in the animal facility of the hospital for at least 1 week prior to the start of the study to allow them sufficient time for acclimatization. The local facilities had been inspected by state veterinarians, and the project was approved by the local ethics committee on animal research.

**Anesthesia**

All surgical and bronchologic procedures were performed with the test animals under general anesthesia. Premedication was administered IM with ketamine (15 mg/kg), midazolam (0.3 mg/kg), and atropine (0.03 mg/kg). After insertion of a peripheral IV catheter, anesthesia was induced with IV propofol (2 to 3 mg/kg) followed by a continuous infusion of propofol (6 to 10 mg/kg/h) for maintenance. For the external surgical procedure the mini-pigs were intubated and ventilated in a spontaneous-assisted mode. For the endoscopic procedure the mini-pigs were intubated with a rigid bronchoscope and ventilated with the same mode. Heart rate and oxygen saturation were monitored by pulse oxymetry throughout the procedure. At the end of the operation, extubation was performed as soon as spontaneous respiration was sufficient to maintain oxygen saturation above 90%. During recovery the mini-pigs were warmed with heating lamps. At the end of the final procedure, the animals were killed with an IV bolus injection of 100 mg/kg of pentobarbital.

**Model of Tracheal Stenosis**

The pig model of a tracheal stenosis recently described by Marquette et al\(^{11}\) consisted of a malacic and a fibrous component mimicking the more complicated type of benign postintubation or tracheostomy stenoses in humans. Briefly described, the trachea was exposed via a midline cervical incision above the thoracic inlet; and the ventral 50% of the tracheal cartilaginous rings six through eight were removed extramucosally, which means the trachea was not opened. Two weeks later, during rigid bronchoscopy, a 2-cm smear of a highly caustic solution of NaOH (20%) was applied with a cotton swab at the level of the resected arches. The posterior membrane was spared this treatment to avoid the development of an esophagotracheal fistula. The application was stopped at the first signs of a brownish discoloration of the mucosa. Another 2 weeks later, a second rigid bronchoscopy was performed to assess the degree of tracheal stenosis and to insert the prototype stent, or to perform a second application of NaOH if the degree of the stenosis was < 50% of the normal diameter.

In a pilot series, two mini-pigs died when we used this approach: one asphyxiated when its trachea was totally obstructed by granulation tissue, and the other had a fatal hemoptysis because of caustic erosion of an artery. Furthermore, an exact identification of the flaccid part of the trachea was not done as easily as expected, even with additional pressure on the trachea from outside, because inflammatory reparative changes of the mucosa made the recognition of the tracheal rings quite difficult. We subsequently modified the technique of Marquette et al\(^{11}\); at the end of the resection of the cartilaginous arches, the entire surface was marked with two to three drops of India ink, which indicated the exact extent of the flaccid segment by a bluish halo seen on bronchoscopy 2 weeks later. The application of NaOH was strictly limited to the anterior 50% of the tracheal mucosa, and was stopped when the mucosa turned white before additional brownish discoloration ensued. This led to a less severe reaction resulting in a stable 50% to 70% tracheal stenosis of 2 to 2.5 cm in length, and no respiratory distress in the animals (Fig 1). Only when feeding did some of the mini-pigs exhibit a slight stridor without any signs of distress. We applied this modified technique to the series of 12 mini-pigs used in our testing of the new stent.
**Stent Prototypes and Insertion Technique**

The new Polyflex stent consisted of a polyester wire mesh embedded in a silicone covering. For insertion it was compressed, resulting in an elongation similar to the well-known Wallstent or its covered version, the Airway Wallstent used in the tracheobronchial tree. For our stenosis model we chose a stent with unconstrained dimensions of 16 mm in diameter and 40 mm in length. This was thought to be adequate for a stenosis of about 12 mm after dilatation with the rigid bronchoscope. The application device consisted of a hollow plastic tube that served as a stent carrier (Fig 2). The stent was supplied in its unconstrained diameter and was loaded into the carrier by the stent charger/pusher, a solid plastic rod with a wire mesh cone attached to one end. The stent was half-way inserted into the cone, and then the cone and stent were gradually compressed and elongated as they were pulled into the carrier. To release the stent from the charger, a conical stent stopper was wedged into the distal end of the stent and the stent charger was pulled vigorously through the carrier, freeing the stent from the wire mesh basket. The stent carrier was then advanced through the rigid bronchoscope until its tip lay just distal to the stenosis. The retrieval of the stent carrier is performed while the pusher remains immobile, freeing the stent, which expands in the stenosis and fits the varying airway diameter snugly, as seen with an hour-glass stenosis.

Two versions of the Polyflex stent were tested: one version had an almost smooth outer surface, and the other version had additional spikes on its outer surface but not at the ends. These spikes were designed to improve anchorage in the mucosa (Fig 3). Five mini-pigs were given smooth stents, and five were given spiked stents. Both ends of each stent exceeded the length of the stenosis by approximately 5 mm. In two of the animals, a longer stenosis necessitated the insertion of an additional stent overlapping the first stent. Of the additional stents one was smooth, and the other one had spikes. The remaining two mini-pigs served as controls, and they were given 12 × 35-mm Dumon silicone stents.

**Figure 1.** An endoscopic view of the proximal end of a tracheal stenosis of 50% to 70% of the normal tracheal diameter in a mini-pig.

**Figure 2.** A schematic illustration of the technique of loading the Polyflex stent into the delivery system and inserting it into a stenotic airway. Top, a: An unconstrained Polyflex stent is introduced half-way into the wire mesh cone of the stent charger, shown slightly protruding from the stent carrier. Top middle, b: The compressed and elongated stent in the stent carrier is secured with a conical stent stopper and freed from the wire mesh cone by a vigorous pulling on the stent charger. Bottom middle, c: The stent carrier containing the compressed stent and the stent pusher located behind the proximal end of the stent is advanced through the rigid bronchoscope until its tip lies distal to the stenosis. Bottom, d: The retrieval of the stent carrier is performed while the pusher remains immobile, freeing the stent, which expands in the stenosis and fits the varying airway diameter snugly, as seen with an hour-glass stenosis.

**Figure 3.** The two prototypes of the Polyflex stent tested. Both stents measured 16 mm in diameter by 40 mm in length. *Left:* A stent with a rough outer surface with additional spikes for better anchorage. *Right:* A stent with a smooth outer surface.
Before stent placement, the stenotic segment was first dilated with a balloon and then gently passed with the tip of a 12-mm outer-diameter rigid bronchoscope (Storz GmbH; Tuttingen, Germany). The stent carrier was then advanced to the tip of the rigid bronchoscope, which was then pulled back about 6 cm, and the stent was then freed as described above. The stent opening was assessed endoscopically and, when necessary, gentle additional dilatation with a forceps or a balloon was performed. At the end of the procedure, a slight pull at the proximal end of the stent was exerted to test anchorage.

Follow-up and Outcome Evaluation

All of the mini-pigs were monitored daily for signs of respiratory distress—coughing, stridor, and tachypnea—as well as changes in weight or feeding habits. The duration of the experiment was planned to be a maximum of 3 months in order to evaluate short-term stent performance and long-term tissue tolerance. Following stent insertion, monthly routine bronchoscopies were planned, as were additional bronchoscopies if warranted by clinical signs. If follow-up bronchoscopy revealed that a stent had migrated, it was exchanged. If excessive granulation tissue formation occurred on stent ends, the tissue was removed mechanically. If the situation was judged to be irreparable, the animal was killed at the end of the procedure with an IV injection of pentobarbital. For the postmortem examination, the lung, trachea, and esophagus up to the glottis were removed in a single block and examined histologically.

RESULTS

The use of our modified experimental model resulted in an easily dilated, stable tracheal stenosis of 50% to 70% of the normal diameter in all of the test animals. A repeat application of NaOH was necessary on two occasions because of an insufficient degree of stenosis, but excessive granulation tissue formation with severe respiratory distress and sudden unexpected suffocation was avoided. Balloon dilation of the stenotic passage prevented the rigid bronchoscope from shearing off mucosa and granulation tissue, and thus prevented any bleeding.

A summary of the most important stent-related results is provided in Table 1. The loading of the stents into the stent carrier was not accomplished as easily as expected. Sometimes the stents did not elongate in a tubular fashion and folded inward, and their reopening was made more difficult because some of the polyester wires were kinked. This problem was more prevalent in the stents with spikes; there was an increased tendency to fold in through the additional wall thickness at the spike level. However, stent deployment and expansion were achieved in all of the test animals, and the stents fitted the airway walls snugly (Fig 4). The overlapping stents placed in the two mini-pigs with longer stenoses fitted perfectly into each other. The overlapping area did not protrude noticeably into the lumen because of the thin wall thickness of the Polyflex stent. None of the stents moved when gently pulled by a forceps, and the procedure could thus be terminated with the stents in place in all of the test animals.

Twenty-four hours after stent placement, the slightly stridorous breathing when feeding had disappeared in all of the mini-pigs. Over a mean observation period of 24 days (range, 10 to 41 days) all of the test animals redeveloped increasing stridor, first when feeding and later while walking. Three of them died unexpectedly from suffocation; in all three a smooth stent had migrated proximally, leading to total obstruction of the artificially induced stenosis. In all, five of the six smooth stents migrated, and only one of the six spiked stents migrated. There was, however, considerable granulation tissue formation at the stent ends, exceeding 50% of the normal airway diameter (Fig 5). In both of the control mini-pigs, the Dumon stent migrated partially (± 1 cm), but less than the smooth Polyflex stents; and in one of the two controls, excessive granulation tissue formation at the stent ends necessitated emergency bronchoscopy. The other control mini-pig developed an approximately 70% fibrotic stenosis at the distal stent end. At the end of the observation period, all of the stents could be removed easily and were found not to have deteriorated over time.

Histologically, the granulomatous reaction at the stent ends was confirmed for the Polyflex and the Dumon stents (Fig 6).

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<th>Table 1: Summary of Technical Aspects and of Short- and Long-Term Effects of Two Polyflex Stent Prototypes in Comparison with Dumon Control Stents in a Pig Model of a Tracheal Stenosis</th>
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Discussion

In this study we were able to adapt successfully the experimental pig model of a tracheal stenosis as described by Marquette et al,¹¹ and to prove its usefulness in evaluating all technical aspects of the new self-expandable Polyflex stent. Contrary to the short-term study of Marquette et al,¹¹ we planned a stent experiment of 3 months duration and, therefore, wanted to have adult animals with fully grown airways. For this purpose mini-pigs presented several advantages. At 18 months they were much smaller than normal pigs, and their tracheobronchial trees were the size of adult animals. At this age their tracheal diameters measured approximately 15 mm, permitting the use of instruments and stents designed for human adults.

In order to obtain a stable degree of tracheal obstruction without respiratory compromise, the stenosis model was modified slightly: the initial flaccid segment was marked more clearly with India ink, and the caustic agent (NaOH) was applied more carefully and more sparingly. Aside from these changes, the experimental model of Marquette et al¹¹ proved to be excellent in testing the technical aspects of insertion, removal, and early tolerance of stents.

The application device had some shortcomings because some of the stents—especially the ones with additional spikes on the outside—tended to fold in, instead of elongating in tubular fashion when compressed and loaded into the stent carrier. To avoid this difficulty, a central thin catheter should be added at the level of the wire mesh basket, which should prevent the stent from folding when it is compressed and elongated. The results of the study clearly show that the smooth-surface prototype tends to migrate (five of six stents migrated), and that stents having retaining spikes prevented this complication (one out of six migrated). These findings were the main benefit derived from our study, as it will obviate the need to test smooth Polyflex stents in benign human airway stenoses.

For at least 10 days all of the mini-pigs were asymptomatic, without stridor, coughing, or increased...
sputum production. This proved that early tolerance and mucus clearance were not problems. Unfortunately, our results were quite disappointing in the long run because all of the mini-pigs redeveloped stridor, a situation that necessitated additional bronchoscopies in 9 of the 12 animals. In the six mini-pigs that had stent migration, stridor was a result of severe obstruction at the level of the original stenosis and was more pronounced than it was before bronchoscopic dilation. In the remaining six animals (four having Polyflex stents, and two having Dumon stents) recurring stridor was clearly a result of the formation of granulation tissue, as it also was with one of the Dumon stents that had partially migrated. Marquette et al.\textsuperscript{11} described similar problems occurring with different stent models in his experiments, with none of the animals surviving with a stent for > 2 weeks. In our study, the extent of granulation tissue formation with both the Polyflex and the Dumon stents was clearly more pronounced than what has been our own experience when using the Dumon stent in humans with similar benign stenoses. This is in accordance with a recent report by Martinez-Ballarin et al.\textsuperscript{12} who confirmed the good tolerance of the Dumon stent in a series with 63 patients who had benign tracheobronchial stenoses, only 4 of whom (6.3\%) developed granulation tissue. We therefore speculate that it is primarily the mini-pig model that leads to more severe long-term reactions than generally occur in humans.

Wassermann et al.\textsuperscript{13} reported the first results of the use of Polyflex stents in humans, and major granulation tissue formation was not observed with 21 stents in 11 patients. In that study, however, 9 of the 11 patients suffered from malignant disease, a factor that precludes direct comparison with benign situations. The question of whether the important granulation tissue formation in the mini-pigs was a result of the Polyflex stent per se, or whether mini-pigs tend to produce granulation tissue more readily than humans cannot be answered unequivocally with the currently available data. Long-term tolerance of stents in benign airway obstruction might be difficult, or even impossible, to test with our current animal model.

The high migration rate of the smooth-surface Polyflex stent seems to confirm our assumption that covered stents do not anchor sufficiently by means of their radial expansion force alone, but need additional mechanical studs, spikes, hooks, or rings to prevent migration. We made similar observations with the Airway Wallstent, a self-expandable covered metal stent. Contrary to the Polyflex stent, the Airway Wallstent has sharp wire ends protruding from the covering at both ends on compression. These wire ends prevent stent migration by lodging in the mucosa.\textsuperscript{14} Our migration rate with the smooth Polyflex prototype was clearly higher than that reported by Wassermann et al.,\textsuperscript{13} who cited only two dislocations in 21 smooth-stent insertions; but the high percentage of malignant disorders in that series does not allow direct comparison with our study.

We conclude that the modified experimental fibromalacic stricture of Marquette et al.\textsuperscript{11} is a useful model of a tracheal stenosis to test all short-term technical aspects of stents. This obviates the need to test them directly in humans. Of the two Polyflex stent prototypes tested, the one with spikes on the outer surface helped to prevent migration and makes this stent look promising. Long-term compatibility, however, seems to be difficult or even impossible to test with our model, as both the Polyflex and the Dumon stents led to excessive granulation tissue formation at the stent ends, a factor which—in the case of the Dumon stent—does not occur to such a degree in benign human airway stenoses. Lacking a perfect animal model for testing long-term stent tolerance, clinical trials in humans will have to assess this aspect of the Polyflex stent.

\textbf{REFERENCES}