Prolongation of patency of airway bypass stents with use of drug-eluting stents

Cliff K. Choong, FRACS, a Loc Phan, BSC,b Patrick Massetti, BSC,b Fabio J. Haddad, MD,a Carlo Martinez, MD,a Edmund Roschak, BSC,b and Joel D. Cooper, MDa

Objective: Airway bypass by transbronchial fenestration has been shown to improve forced expiratory volume and flow in explanted emphysematous human lungs. We previously demonstrated the feasibility and safety of airway bypass stent placement in a canine model, but we found that most stents occluded within 1 week. The aim of this study was to evaluate the influence of controlled-release paclitaxel-eluting stents on prolongation of patency.

Methods: With the subject dogs under general anesthesia, suitable segmental and subsegmental bronchial wall sites were selected by direct visualization with a flexible bronchoscope. A Doppler probe was used to detect and avoid sites with adjacent blood vessels. Transbronchial passages were formed with a 25-gauge transbronchial needle-tipped catheter and dilated with a 2.5-mm balloon integrated into the needle catheter. A specifically designed expandable stainless steel stent (3 mm long × 3 mm wide) embedded in a sleeve of silicone rubber was placed within the passage and expanded until secured about the bronchial wall. Fifty control stents (no paclitaxel impregnation) and 107 paclitaxel-eluting stents were placed in 25 dogs. Animals underwent bronchoscopy at intervals to assess stent patency.

Results: Eight instances of minor and brief bleeding occurred during stent placement; all resolved without incident. There were no pneumothoraces or deaths associated with stent placement. No delayed complications occurred. No identifiable paclitaxel-related toxicity was observed. At 1, 4, 8, and 12 weeks, the patency rates were 10%, 0%, 0%, and 0% for control stents and 100%, 96%, 76%, and 65% for paclitaxel stents.

Conclusion: In an animal model, the use of specifically designed paclitaxel-eluting airway bypass stents was both feasible and safe. These stents resulted in a significant prolongation of patency.

Collateral ventilation, the ability of gas to move from one part of the lung to another through nonanatomic pathways, was first observed by Van Allen and colleagues in 1930. The importance of collateral ventilation is minimal in normal lungs, because the resistance to air flow is higher in collateral channels than in the airway. However, the resistance of air flow in collateral channels is low in patients with emphysema relative to that in normal lungs. In emphysematous lungs, collateral ventilation provides important channels for gas distribution and may be therapeutically useful. We have previously demonstrated that creation of direct passages between emphysematous pulmonary parenchyma and bronchial airways (airway bypass) in excised emphysematous human lungs can improve expiratory flow and volume, which is otherwise limited by the collapse of the small, peripheral airways during expiration. Our ex vivo study of 12 emphysematous human lungs demonstrated that creation of three passages improved mean forced expiratory volume in 1 second from 245 mL to 447 mL. The addition of two more passages further improved mean forced expiratory volume in 1 second to 666 mL.
We subsequently demonstrated that airway bypass passages can be safely created in patients with emphysema. In a separate animal study, we showed that it was feasible and safe to place airway bypass stents in vivo. Most of the stents, however, became occluded within 1 week after placement, and this would pose a major problem for potential clinical application. The topical application of mitomycin, an anti-inflammatory and antifibrotic agent, has been reported to be useful in the treatment of airway stenosis. We evaluated the influence of weekly topical mitomycin on airway bypass stent patency and found it to prolong stent patency. However, it is not practical to subject patients to weekly bronchoscopic topical application of mitomycin to prolong stent patency. The aim of this study was therefore to evaluate the influence of controlled-release paclitaxel-eluting stents on prolongation of airway bypass stent patency.

Materials and Methods
Specially bred research mongrel dogs were used for the experiment. The weights of the dogs were between 20 and 25 kg. The airway bypass procedure was performed with the animals under general anesthesia, and each dog was mechanically ventilated via a single-lumen endotracheal tube. The equipment used is shown in Figure 1. A standard 4.9-mm external diameter flexible fiberoptic bronchoscope with a 2-mm working channel (BF-P160; Olympus America Inc, Melville, NY) was used to visualize the airway and to select appropriate target sites at the segmental or subsegmental bronchial level. A Doppler catheter (Broncus Technologies Inc, Mountain View, Calif) inserted through the bronchoscope channel was used to scan the target site and its adjacent area to detect and to avoid peribronchial vessels before transbronchial fenestration. Once an appropriate site had been identified, the Doppler probe was exchanged for a 25-gauge transbronchial retractable needle-tipped catheter with a 2.5-mm balloon integrated into the catheter. Transbronchial passages were formed with the 25-gauge transbronchial needle and dilated with the integrated 2.5-mm balloon. The needle-balloon catheter was withdrawn, and a balloon-expandable stent was passed through the bronchoscope channel and visually positioned in the newly created passage. The paclitaxel-eluting stent used is made of stainless steel (3 mm long/3 mm wide) embedded within silicone rubber impregnated with paclitaxel (Exhale Stent; Broncus Technologies). This stent expands out on either end from its midportion (3 mm wide) to a 5.5-mm flange that helps to secure the stent (Figure 1). Fifty control stents (no paclitaxel impregnation) and 107 paclitaxel-eluting stents were placed in 25 dogs. Each paclitaxel-eluting airway bypass stent contains approximately 400 μg paclitaxel. Most of the released drug is delivered within the first 90 days.

Animals underwent bronchoscopy at intervals to assess stent patency. The stent was considered to be occluded if there was tissue ingrowth that completely filled the inside channel of the stent for at least half its length. The general health status of the dogs was assessed by daily clinical examination and weekly complete blood count, urea, and electrolyte laboratory blood tests. Weekly follow-up was performed to a maximum of 18 weeks. The study had animal studies ethics committee approval. All animals received humane care in compliance with the “Guide for the Care and Use of Laboratory Animals” (http://www.nap.edu/catalog/5140.html).

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<thead>
<tr>
<th>Week</th>
<th>Control stents (%)</th>
<th>Paclitaxel-eluting stents (%)</th>
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<tr>
<td></td>
<td>No.</td>
<td>%</td>
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<tr>
<td>1</td>
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<td>18</td>
<td>23/35*</td>
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*After the 12th week of follow-up, 16 dogs were killed and the remaining 9 dogs were followed up until the 18th week, per the study protocol.
Results
Eight episodes of minor and brief bleeding occurred during transbronchial passage formation. These were treated with dilute topical epinephrine solution and resolved without incident. There were no pneumothoraces or deaths associated with stent placement. No delayed hemorrhages or pneumothoraces occurred. The animals remained clinically well throughout the study period, and there were no abnormal laboratory blood test results. Ninety percent of the control stents were found to be occluded at the first week of bronchoscopic follow-up, and the rest were occluded by the fourth week of follow-up (Table 1). In contrast, paclitaxel-eluting stents had a significant prolongation of stent patency (Table 1, Figure 2). The median duration of stent patency in the paclitaxel group was greater than 18 weeks, because approximately two thirds of the paclitaxel-eluting stents were still patent at the 18-week conclusion of bronchoscopic follow-up. Examples of patent and occluded stents, as visualized with bronchoscopy, are shown in Figure 3.

Discussion
Emphysema is anatomically defined as irreversible increase in the size of the air spaces distal to the terminal bronchioles, resulting from the destructive activity of neutrophil and macrophage elastase. It is associated with a loss of lung elastic recoil and progressive dynamic hyperinflation of the lungs. These changes result in enlargement of the thorax, flattening of the diaphragm, increased work of breathing, increased dyspnea, and reduced exercise tolerance. The progressive loss of elastic recoil traps the patient in a state of hyperinflation in which forced expiratory effort cannot reduce the residual volume, because the force exerted to empty the lungs collapses the small airways and obstructs the outflow of gas. Progressive hyperinflation of the lungs and hyperextension of the chest wall also diminish inspiratory capacity. To maintain adequate minute ventilation, the respiratory rate must increase, resulting in an increase in the work of breathing and in dyspnea.

Surgical options in the treatment of emphysema include lung transplantation and lung volume reduction surgery. Both treatment modalities have specific indications, and their use is limited to selected patients. Our group embarked on an experimental study of airway bypass with the goal of developing a palliative treatment for patients with homogeneous severe emphysema who are not candidates for either lung transplantation or lung volume reduction surgery. We previously found that the creation of extra-anatomic bronchopulmonary passages in ex vivo emphysematous lungs resulted in the improvement of forced expiratory flow and

![Kaplan-Meier freedom from stent closure](image1.png)

**Figure 2.** Kaplan-Meier freedom from stent closure.

![Examples of patent and occluded stents visualized on bronchoscopy](image2.png)

**Figure 3.** Examples of patent and occluded stents visualized on bronchoscopy. a, Stent at time of placement. b, Occluded control stent at 1 week of follow-up. c, Patent paclitaxel-eluting stent at 3 weeks of follow-up. d, Patent paclitaxel-eluting stent at 13 weeks of follow-up.
volume. The transbronchial passages created took advantage of the extensive collateral ventilation present in emphysematous lungs to allow additional removal of trapped gas and further reduction of residual volume not obtainable through the airways. The airway bypass stent was developed as a noncollapsing structure that would prevent the collapse and closure of these transbronchial passages. We initially used a radiofrequency probe to create the transbronchial passages, but we subsequently altered the technique to use a 22-gauge needle to create the transbronchial track and a 2.5-mm dilating balloon to expand the puncture site. We now use an integrated needle-balloon device, as described in this article. This combined device has resulted in a significant ease, simplicity, and time saving in the formation of the transbronchial passages.

Paclitaxel has been successfully applied to the prevention of coronary artery restenosis and works by inhibiting mitosis and prevention of neointimal proliferation while allowing healing and endothelialization. In the prevention of coronary artery in-stent stenosis, paclitaxel is considered to be best delivered locally on a drug-eluting stent to achieve therapeutic concentrations without the risk of systemic toxicity. On the basis of these findings, we chose to assess the potential effect of paclitaxel-eluting stents on airway bypass stent patency. Our results suggest that paclitaxel was effective in maintaining airway bypass stent patency. The potential clinical application of an effective drug-eluting airway bypass stent is that it would obviate the need for patients to undergo regular bronchoscopic topical application of medications to maintain airway bypass stent patency. Paclitaxel-eluting coronary stents have been found to be safe and without significant adverse effects, with the local delivery minimizing the risks of systemic toxicity. Paclitaxel is widely used as an effective anticancer chemotherapeutic agent, for which purpose it has been administered systemically at dosages in the range of 135 to 300 mg/m2 with satisfactory patient tolerance.

In summary, it was feasible and safe to perform airway bypass stent placement in vivo. In our canine model, most control stents became occluded within 1 week. Placement of paclitaxel-eluting airway bypass stents, however, resulted in a prolonged duration of stent patency.

We thank Patricia Toenskoetter, Naomi Still, and Katheryn Cook for their technical assistance in the project.

References


Discussion

Dr Steven J. Mentzer (Boston, Mass). We now have three major approaches to the endobronchial treatment of emphysema. The first is the bronchial valve, essentially a 1-way valve designed to induce distal atelectasis. The second is the instillation of bioactive agents to induce distal atelectasis and scarring. These two approaches are designed to reduce lung volumes. The third approach, presented here, is conceptually different. It relies on collateral ventilation to bypass obstructed airways and improve expiratory flow.

A central question regarding this third approach to endobronchial treatment of emphysema is collateral ventilation in human beings. It’s interesting, Dr Choong, that you chose the dog model. In pigs, as you may know, there is little if any collateral ventilation. The lobules in a pig lung prevent collateral ventilation. In dogs, there are essentially no fibrous septa, and the lung is basically unlobulated. In human beings, the situation is somewhere in
between. Could you comment on how dependent your results are on the dog model?

Dr. Choong. The purpose of this study was to assess the patency of paclitaxel-eluting airway bypass stents in a dog model. As previously mentioned, the dogs used in the study were normal dogs with normal lungs. We have previously provided the definition of an occluded stent as one with tissue ingrowth occupying half or more of the stent channel. The patency of the stents was therefore assessed in accordance with that definition. The purpose of this study was not to assess the effects of airway bypass stents on collateral ventilation. These normal dogs had normal lungs and therefore did not have significant collateral ventilation. Collateral ventilation is present in human beings and is especially significant in patients with emphysematous lungs. We believe that the airway bypass stents would take advantage of that situation and improve expiratory flow and volume in patients with emphysema. We have done experimental studies with explanted emphysematous human lungs obtained from lung transplant recipients during lung transplantations, with patient and ethics committee approval, and these studies demonstrated that airway bypass stents do take advantage of the significant collateral ventilation that is present in emphysematous lungs, leading to improvement in expiratory flow and volume and reduction in hyperinflation. Preliminary clinical studies in human patients have also confirmed these results.

Dr Mentzer. However, one would imagine that if you have collateral ventilation, the chance of having continuous ventilation and a patent stent would improve. Conversely, if you have distal atelectasis, the amount of ventilation distal to the stent would be diminished.

A related point regards the time constant of the stents. If the amount of time that it takes for air flow to go across the stent is relatively large relative to the ventilatory cycle, then the contribution of those stents to overall ventilatory function would be small. Clearly, the time constant is dependent on stent patency. As these stents start to occlude, you would expect the time constant to go up and the relative benefit of the stent to go down.

Dr. Choong. Exactly. I think one of the critical issues for this to be successful is to ensure that the stents stay patent.

Dr. Choong. It seems logical that if the stents are truly decompressing distal emphysematous lung, you might affect distal hyperinflation. For example, dynamic hyperinflation might be less and air flow improved with these additional air passages. Do you have any evidence, in animals or in human beings, that dynamic hyperinflation is in fact improved with stent therapy?

Dr. Choong. We are currently conducting experimental studies specifically looking at this area, together with Drs Peter Macklem, John Pierce, and Jim Hogg. In our studies, the airway bypass stents resulted in improvement in the physiologic and mechanical properties of explanted emphysematous human lungs. Preliminary clinical studies in human patients have confirmed these results.

Dr. Choong. In terms of looking at the blood gas values, we have not done this in the experimental or clinical studies that we’re conducting. In our experimental and clinical studies, however, the airway bypass stents did result in a decrease in the trapped gas and the residual volumes of emphysematous lungs.

Dr Joseph B. Shrager (Philadelphia, Pa). This was a nice presentation of obviously exciting work. I’m particularly excited to see the picture you presented from the human lung, which is the first one I’ve seen where you can actually visualize the lung parenchyma directly through the hole; on the other hand, in the pictures that you showed in the animals, at least the ones you presented here today, it’s not entirely clear to me that you can tell objectively whether the stent is open. Is it a “plus/minus” obvious event whether the thing is open?

Dr. Choong. Yes. The picture I showed of the airway bypass stent that was placed in a patient with severe emphysema shows clearly the appearance of a patent stent and the markedly destroyed emphysematous lung seen through the stent channel.

Dr. Shrager. Isn’t there a degree of subjective interpretation as to whether a stent has remained open? If it is a little bit subjective, is there something else you can do to make sure they are in fact open? Are there any adjunctive things that you are doing bronchoscopically to tell whether they are really open?

Dr. Choong. In the animal studies that we conducted, we used normal research mongrel dogs with normal lungs. They did not have emphysematous lungs. Therefore, in the pictures I have shown, you’re looking at solid lung parenchyma at the other end of the stent channel. The way we define stent occlusion is that half or more of the stent channel is occupied by tissue. You are right that in emphysematous human lungs there is a definite, clear view of the destroyed lung tissue; unfortunately, we do not have this situation in the normal research mongrel dogs with normal lungs.

Dr. Shrager. So you are not really sure whether there is air flowing back and forth through these stents that you’re calling open?

Dr. Choong. There is most likely no air flow in these normal lungs, but the purpose of this study was to look at the patency according to the definition previously described. We have, however, used the paclitaxel-eluting airway bypass stents in human clinical studies, and we have found encouraging results with these stents being patent and looking that way during follow-up.

Dr. Shrager. For how long do they elute paclitaxel?

Dr. Choong. Most of the elution occurs though a 3-month period.