Clinical application of airway bypass with paclitaxel-eluting stents: Early results

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Objective: To assess the safety and early clinical results of a multicenter evaluation of airway bypass with paclitaxel-eluting stents for selected patients with severe emphysema.

Methods: Airway bypass was performed with a fiberoptic bronchoscope in three steps: identification of a blood vessel-free location with a Doppler probe at the level of segmental bronchi, fenestration of the bronchial wall, and placement of a paclitaxel-eluting stent to expand and maintain the new passage between the airway and adjacent lung tissue. All adverse events were recorded, as well as 1- and 6-month pulmonary function tests and dyspnea index.

Results: Thirty-five patients received the airway bypass procedure with a median of 8 stents implanted per patient. At 1-month follow-up, statistically significant differences in residual volume, total lung capacity, forced vital capacity, forced expiratory volume, modified Medical Research Council scale, 6-minute walk, and St George's Respiratory Questionnaire were observed. At the 6-month follow-up, statistically significant improvements in residual volume and dyspnea were demonstrated. One death occurred after bleeding during the procedure. Retrospective analysis revealed that the degree of pretreatment hyperinflation may be an important indicator of which patients achieve the best short- and long-term results.

Conclusions: The airway bypass procedure reduces hyperinflation and improves pulmonary function and dyspnea in selected patients with severe emphysema. Duration of benefit appears to correlate with the degree of pretreatment hyperinflation. These preliminary clinical results support further evaluation of the procedure.

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The irreversible destruction of lung parenchyma in emphysema is characterized by progressive air space enlargement within the lung and is associated with marked enhancement of collateral ventilation. The concept of collateral ventilation was first introduced by Van Allen, Lindskog, and Richter¹ in 1930. Collateral ventilation is inconsequential in normal human lungs; however, in emphysematous lungs it can be essential for ventilation distribution beyond the obstructed airways.² In emphysema, the resistance of the airways can exceed collateral resistance, forcing air to flow preferentially through collateral pathways, which may ultimately promote the redistribution of ventilation within the lungs.³ Revisiting this concept in 1978, Macklem⁴ proposed its potential clinical applicability for reducing gas trapping by venting the hyperinflated emphysematous lungs through spiracles—the creation of artificial passages from the lung surface to the outside of the chest. A recent revision of this lung deflation concept proposed bronchial fenestration for venting the emphysematous air spaces into the main airway, coining the term “airway bypass.”⁵ Airway bypass is the process of creating extra-anatomic passages between the collaterally ventilated pulmonary parenchyma and larger airways, allowing trapped gas to exit from the lung. This decrease in gas trapping reduces hyperinflation, allowing better chest wall and diaphragmatic excursion and therefore improving dyspnea. The feasibility of airway bypass was first tested experimentally on ex vivo explanted native lungs obtained from patients with emphysema undergoing lung transplantation.⁶ This study demonstrated an improvement in the forced expiratory volumes in 1 and 5 seconds (FEV₁ and FEV₅), thus suggesting airway bypass as a potential therapeutic option for patients with marked hyperinflation and severe pulmonary destruction. These early clinical feasibility and safety studies in human lungs^{5,7} recognized, but did not address, the need to develop the technology to improve long-term passage patency. Other laboratory research studied the value of combining stents with pharmaceuticals to inhibit tissue growth around the stent.⁷ This, in turn, resulted in the development of the paclitaxel-eluting stent, which significantly prolonged stent patency in animals.⁸ On the basis of these advances, the current research was undertaken to assess the safety and short-term clinical results of the airway bypass procedure using paclitaxel-eluting stents. It evaluates the applicability of the procedure to a multicenter study while suggesting an optimum target group for future clinical studies.

Patients and Methods

Patients with emphysema were enrolled in the study according to the following major criteria: computed tomographic scan evidence of bilateral emphysema; post-bronchodilator residual volume (RV) 220% or more of predicted; post-bronchodilator total lung capacity (TLC) 133% or more of predicted; post-bronchodilator FEV₁ 40% or less of predicted or FEV₁ of less than 1 L; dyspnea scoring of 2

Abbreviations and Acronyms

COPD	= chronic obstructive pulmonary disease
FEV ₁ , FEV ₅	= forced expiratory volumes in 1 and 5 seconds
FVC	= forced vital capacity
6MW	= 6-minute walk
mMRC	= modified Medical Research Council
NETT	= National Emphysema Treatment Trial
RV	= residual volume
SGRQ	= St George's Respiratory Questionnaire
TLC	= total lung capacity

or more according to the modified Medical Research Council (mMRC) scale; arterial oxygen tension of 45 mm Hg or more on room air; and subjects who signed an informed consent form, were compliant, judged not suitable for other interventions, and considered fit to undergo a procedure under general anesthesia. Major exclusion criteria were the following: inability to walk more than 140 m at level in 6 minutes after pulmonary rehabilitation; presence of pulmonary hypertension (peak systolic pressure of >45 mm Hg or mean pressure of >35 mm Hg) as documented by 2-dimensional echocardiogram or right heart catheterization; any previous pulmonary resection; coronary artery disease with angina; history of myocardial infarction within 6 months or stroke less than 1 year before the procedure; insulin-dependent diabetes; unequivocal lung cancer or the presence of suspicious pulmonary nodule/infiltrate; large bullae; ventilator dependence; alpha-1 antitrypsin deficiency; coagulation disorder; steroid therapy of 20 mg prednisone or more per day; unequivocal and symptomatic bronchiectasis; and 3 or more respiratory infections requiring hospitalization within the past 12 months. Subjects who met the criteria underwent a pulmonary rehabilitation program of 16 to 20 sessions over 6 to 10 weeks, ending no greater than 6 weeks before the procedure. Rehabilitation resumed after the procedure for up to 8 weeks and was then encouraged but not required. Within 24 to 48 hours before the procedure, all subjects underwent a chest computed tomographic scan, spirometry, body plethysmography, and dyspnea scoring (baseline measurements). Subjects received intravenous antibiotics starting on arrival at the operating room. The airway bypass procedure was performed with the patient under general anesthesia with orotracheal intubation and controlled mechanical ventilation. The Exhale Emphysema Treatment System (Broncus Technologies, Inc, Mountain View, Calif) has 4 components: (1) the Exhale Doppler Probe, which is a catheter with a 1.4-mm ultrasonic Doppler transducer at the distal tip; (2) the Exhale Doppler Processing Unit, which amplifies the sounds of the Doppler probe; (3) the Exhale Transbronchial Dilatation Needle, which is a combination 25-gauge needle and 2.5-mm dilation balloon catheter for passage creation and dilation; and (4) the Exhale Drug-Eluting Stent (3.3-mm inner diameter, 5.3-mm outer diameter, 2 mm in length) with paclitaxel embedded within the silicone layer mounted on a delivery balloon catheter (Figure 1). All these catheters were designed to pass through the 2 mm or larger working channel of a flexible bronchoscope. The system uses a standard, commercially available inflation syringe to inflate

Figure 1. Devices used for airway bypass: A, Exhale Doppler Probe; B, Exhale Transbronchial Balloon Dilation Needle; C, Exhale Drug-Eluting Stent mounted on delivery catheter; D, Exhale Drug-Eluting Stent deployed.

the balloons on the balloon catheters. Airway bypass was performed in a single session with a flexible bronchoscope. Efforts were made to place a minimum of 2 stents in each upper and lower lobe bilaterally. The middle lobe was not treated. Creation of each stented passage required 3 steps: (1) identification of a blood vessel-free location with a Doppler probe at the level of segmental bronchi; (2) fenestration of the bronchial wall using the transbronchial needle and dilating balloon; and (3) placement of a paclitaxel-eluting stent to hold the passage open. After stent placement, the subject was allowed to recover from anesthesia, a routine chest radiograph was performed in the recovery room, and the subject was returned to the hospital room the same day. Intravenous antibiotics were continued for the first 24 hours after the procedure until discharge from the hospital, when they were switched to an oral route for 7 consecutive days. Follow-up visits were scheduled for 30, 60, 90, 135, and 180 days after the procedure. Parameters measured were RV, TLC, forced vital capacity (FVC), and FEV₁. Key functional measurements were mMRC, 6-minute walk (6MW), and St George's Respiratory Questionnaire (SGRQ). Safety was assessed through the solicitation of adverse event reports. Safety stopping rules included the following: 3% procedure-related death; 30% postprocedure pneumothorax requiring chest tube drainage for more than 7 days; 3% pulmonary bleeding requiring transfusion; and 15% worsened ventilatory status resulting in the need for mechanical ventilation.

Statistical Analysis

Statistical analysis included several summary statistics for changes in the following parameters with respect to baseline: RV, TLC, FVC, FEV₁, mMRC, 6MW, and SGRQ. The descriptive statistics included the number of nonmissing values, mean, and standard deviation at the 1- and 6-month visits. The statistical significance of differences from baseline was assessed by a 2-sided *t* test that paired visit values with baseline values. The median

baseline RV/TLC ratio was used to stratify subjects into 2 groups to assess impact of airway bypass on the test parameters at 6 months.

Results

A total of 35 subjects at 7 centers completed the airway bypass procedure between July 2004 and October 2005. There were 19 men and 16 women with ages between 45 to 81 years (average 62 years). The majority of subjects (33/35; 94%) had homogeneous emphysema. A total of 264 stents were implanted successfully (median of 8 stents per subject, with a range of 2 to 12 stents). Three additional subjects were selected for, but did not complete, the procedure. One subject did not have stents implanted due to the abundance of blood vessels adjacent to the airway walls as detected by Doppler. In another subject the thickness of the airways prevented stents from being implanted. One death occurred after intraoperative bleeding during treatment (2.6% of all subjects; 0.4% of all passages made). At the time, this triggered the safety stopping rules for the study. The study was resumed after an extensive Data and Safety Monitoring Board investigation, which generated several modifications. Mean baseline versus 1-month and 6-month follow-up measurements are listed in Table 1. The mean values for all measurements listed showed statistically significant improvement between baseline and 1-month follow-up. At 6 months there was a statistically significant reduction in RV (−400 mL; *P* = .04) and dyspnea (−0.5; *P* = .025).

Subjects were divided into 2 groups, based on whether their baseline RV/TLC ratio was above or below the median (0.67) for the entire cohort. Tables 2 and 3 show the test parameters at baseline, 1, and 6 months for subjects above

TABLE 1. Average values for all subject groups at follow-up time points

Parameter	Baseline (n = 36)	1 Month	Change (P value)*	6 Months	Change (P value)*
RV (L)	5.34 ± 1.13	4.85 ± 0.97	−0.75 L, −12.4% (<.001)	4.98 ± 1.25	−0.40 L, −6.6% (.040)
TLC (L)	7.80 ± 1.27	7.69 ± 1.18	−0.38 L, −4.3% (.017)	7.59 ± 1.48	−0.25 L, −3.0% (.118)
FVC (L)	2.30 ± 0.80	2.51 ± 0.77	17.2% (<.001)	2.31 ± 0.74	8.4% (.332)
FEV ₁ (L)	0.74 ± 0.19	0.79 ± 0.27	7.3% (.038)	0.73 ± 0.23	0.6% (.879)
mMRC (points)	2.7 ± 0.7	2.0 ± 0.9	−0.6 (.003)	2.2 ± 1.1	−0.5 (.025)
6MW (m)	340.9 ± 103.1	378.0 ± 114.2	37.2 (<.001)	326.7 ± 122.3	−12.0 (.297)
SGRQ (points)	57.8 ± 14.9	53.1 ± 16.8	−4.7 (.008)	56.6 ± 17.2	−1.8 (.335)

Data are mean ± standard deviation. L, liters; m, meters; RV, residual volume; TLC, total lung capacity; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; mMRC, modified Medical Research Council; 6MW, 6-minute walk; SGRQ, St George's Respiratory Questionnaire. *Absolute and percent change from baseline reported for RV, percent change from baseline for TLC, FVC, and FEV₁, and absolute change for mMRC, 6MW, and SGRQ. P values are derived from a 2-tailed paired t test for differences from baseline. Average changes only include patients with data for 1 or 6 months.

TABLE 2. Results for patients with baseline RV/TLC above the median of 0.67

Parameter	Baseline (n = 18)	1 Month (n = 16)	Change (P value)*	6 Months	Change (P value)*
RV (L)	5.92 ± 1.21	5.09 ± 1.10	−1.04 L, −16.2% (.001)	5.20 ± 1.56	−0.87 L, −14.1% (.022)
TLC (L)	7.80 ± 1.38	7.41 ± 1.23	−0.61 L, −7.1% (.016)	7.45 ± 1.62	−0.46 L, −5.6% (.120)
FVC (L)	1.78 ± 0.46	2.08 ± 0.50	22.6% (.006)	2.01 ± 0.56	17.8% (.065)
FEV ₁ (L)	0.64 ± 0.16	0.70 ± 0.24	7.9% (.113)	0.67 ± 0.25	4.1% (.396)
mMRC (points)	2.7 ± 0.8	2.0 ± 1.0	−0.7 (.007)	2.2 ± 1.2	−0.5 (.035)
6MW (m)	307.4 ± 106.8	349.7 ± 129.9	44.7 (.002)	306.4 ± 121.8	−1.0 (.948)
SGRQ (points)	57.1 ± 15.3	49.9 ± 19.4	−7.1 (.007)	52.4 ± 18.7	−4.7 (.100)

Data are mean ± standard deviation. L, liters; m, meters; RV, residual volume; TLC, total lung capacity; FVC, forced vital capacity; FEV₁, forced expiratory volume in one second; mMRC, modified Medical Research Council; 6MW, 6-minute walk; SGRQ, St George's Respiratory Questionnaire. *Absolute and percent change from baseline reported for RV, percent change from baseline for TLC, FVC, and FEV₁, and absolute change for mMRC, 6MW, and SGRQ. P values are derived from a 2-tailed paired t test for differences from baseline. Average changes only include patients with data for 1 or 6 months.

TABLE 3. Results for patients with baseline RV/TLC at and below the median of 0.67

Parameter	Baseline (n = 18)	1 Month	Change (P value)*	6 Months	Change (P value)*
RV (L)	4.77 ± 0.68	4.55 ± 0.71	−0.40 L, −7.7% (.048)	4.78 ± 0.86	0.03 L, −0.4% (.723)
TLC (L)	7.80 ± 1.18	8.03 ± 1.05	−0.09 L, −0.9% (.569)	7.72 ± 1.38	−0.05 L, −0.6% (.718)
FVC (L)	2.81 ± 0.75	2.99 ± 0.73	11.1% (.026)	2.67 ± 0.79	−2.9% (.285)
FEV ₁ (L)	0.85 ± 0.17	0.90 ± 0.28	6.7% (.191)	0.81 ± 0.198	−3.6% (.301)
mMRC (points)	2.6 ± 0.7	2.1 ± 0.9	−0.5 (.120)	2.1 ± 1.1	−0.5 (.216)
6MW (m)	374.3 ± 90.1	410.4 ± 86.7	28.6 (.021)	349.5 ± 122.6	−24.4 (.170)
SGRQ (points)	58.6 ± 15.0	56.5 ± 13.5	−2.1 (.374)	61.6 ± 14.3	1.7 (.468)

Data are mean ± standard deviation. L, liters; m, meters; RV, residual volume; TLC, total lung capacity; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; mMRC, modified Medical Research Council; 6MW, 6-minute walk; SGRQ, St George's Respiratory Questionnaire. *Absolute and percent change from baseline reported for RV, percent change from baseline for TLC, FVC, and FEV₁, and absolute change for mMRC, 6MW, and SGRQ. P values are derived from a 2-tailed paired t test for differences from baseline. Average changes only include patients with data for 1 or 6 months.

and below the median, respectively. In subjects with baseline RV/TLC above the median, RV is reduced by 1040 mL (−16.2%; $P = .001$) at 1 month and 870 mL (−14%; $P = .022$) at 6 months. In addition, at 6 months FVC improved by 17% from baseline, which, while not statistically significant, is higher than the 12% improvement that has been identified as clinically significant.⁹ For subjects with RV/TLC at and below the median, RV (−400 mL; $P = .048$), FVC (11.1%; $P = .026$) and 6MW (28.6; $P = .021$) had a

statistically significant improvement at 1 month, but none of the benefits were maintained at 6 months, with most parameters returning to near or below baseline.

Adverse events and complications are summarized in Table 4. Of the 38 treated subjects, 3 (7.9%) experienced intraoperative serious adverse events, including 1 (2.6%) death that was a consequence of major bleeding into the airway. All other bleeding events were minor and controlled locally with topical cold saline and epinephrine solution.

TABLE 4. Serious adverse events recorded after the airway bypass procedure

Serious adverse event	N/total (%)	Early	Late	Outcome
Intraoperative airway bleeding	1/38 (2.6%)	1	—	One death (2.6%)
Intraoperative pneumomediastinum	2/38 (5.3%)	2	—	Resolved spontaneously (no drainage)
COPD exacerbation	12/37 (32.4%)	2	14	Resolved clinically
Respiratory infection	10/37 (27%)	5	5	Resolved clinically
Unstable angina*	1/37 (2.7%)	—	1	Controlled clinically
Bowel obstruction*	1/37 (2.7%)	1	—	One death (2.7%)

N, number of patients who had serious adverse events; *Early adverse event*, less than 30 days after the procedure; *Late adverse event*, more than 30 days after the procedure. *Found to be unrelated to the airway bypass procedure.

The other serious adverse events were pneumomediastinum with subcutaneous emphysema, which occurred in 2 (5.3%) of 38 subjects. One of these events was treated medically (using oxygen therapy, analgesics, and bronchodilators), and the other resolved spontaneously without intervention. Postoperative serious adverse events occurred in 22 (59.4%) of 37 subjects. The 2 most frequently encountered, related serious adverse events were chronic obstructive pulmonary disease (COPD) exacerbations and infection. As is widely known, exacerbations are largely a feature of moderate-to-severe COPD. Sixteen episodes of COPD exacerbation occurred in 12 (32.4%) of 37 treated subjects. However, only 2 of these events occurred within 1 month of treatment and the remainder occurred between 39 and 236 days after treatment (average 144 days). Respiratory infection occurred in 10 (27%) of 37 treated subjects, 5 (13.5%) of these occurred within the first week of treatment, and all were resolved medically. Other related serious adverse events reported as single events included hypercapnia, respiratory failure, and an adverse reaction to naloxone after a scheduled follow-up bronchoscopic examination. Unrelated serious cardiac events were reported in 1 subject, in whom ischemic heart disease and unstable angina developed. One subject had a bowel obstruction that required laparotomy and ultimately died 4 weeks after the operation as a result of infectious complications and sepsis. This event occurred 53 days after airway bypass treatment and death was found to be unrelated to the procedure. Three (8.5%) other subjects were lost to follow-up over the 6-month period.

Although stent potency is not a primary focus of this study, it is an important factor that could affect the clinical results. Follow-up bronchoscopic examinations assessed stent patency in a subset of patients. At 6 months, when 26 site locations were reviewed bronchoscopically, 18 (69%) stents were judged to be patent (Figure 2).

Discussion

The management of emphysema poses a difficult challenge for the medical community inasmuch as the disease progressively deprives patients of their ability to perform activities of daily living and is associated with repeated exacerbations.

Current medical therapies include bronchodilators, steroids, and antibiotics, all directly or indirectly designed to reduce airway resistance to improve respiratory flows and reduce hyperinflation. The long-term results from the National Emphysema Treatment Trial (NETT) confirmed that lung volume reduction surgery, by reducing hyperinflation, can significantly benefit certain patients with emphysema.¹⁰ This has led to exploring less invasive, endoscopic procedures that might produce similar results. "Bronchoscopic lung-volume reduction" with 1-way valves is being evaluated for patients with severe heterogeneous emphysema.^{8,11,12} However, patients with severe homogeneous emphysema are generally not eligible for treatment modalities other than medical management and, in infrequent instances, lung transplantation. Such patients might therefore benefit from a procedure that does not require surgical intervention, reduces hyperinflation, and palliates dyspnea. Airway bypass has been proposed as a procedure that might meet these requirements. It is based on the concept that dynamic distal airway resistance is greatly enhanced in emphysema concurrent with increased collateral ventilation.^{6,13} Choong and associates¹⁴ demon-

Figure 2. Image of an implanted stent at 6-month follow-up fiberoptic bronchoscopic examination.

strated in an animal model that paclitaxel-eluting silicone-covered metal stents significantly extended patency. These findings supported the assumption that paclitaxel-eluting stents could be beneficial for the airway bypass procedure and prompted this initial human study. Paclitaxel is a chemotherapeutic agent administered systemically at dosages in the range of 135 to 300 mg/m² with acceptable patient tolerance. Coronary and airway bypass paclitaxel-eluting stents are loaded with approximately 400 µg of paclitaxel/stent, which is a small fraction of the systemic dose delivered for chemotherapy.¹⁴

There is strong evidence from the results (Table 1) that the mechanism of action by which airway bypass works is a reduction in hyperinflation, measured by a reduction in lung volumes including RV and TLC. The average pretreatment RV in this study population was 5.34 L (257% of predicted normal), which illustrates the severity of gas trapping present in these subjects. Given that the procedure relies on the abundant collateral ventilation found in severely emphysematous lungs, airway bypass would be expected to reduce gas trapping the most in patients with extensive hyperinflation. A statistically significant reduction in hyperinflation, as reflected by RV, was observed throughout the 6-month follow up. This paralleled improvement in dyspnea. However, exercise capacity improvement, as measured by 6MW, was not sustained at 6 months. The cessation of the initial exercise capacity improvement might be due at least in part to the cessation of the perioperative rehabilitation program at 8 weeks. The benefits of rehabilitation before treatment were described in a report from the NETT, which demonstrated its effectiveness in preparing and selecting subjects for lung volume reduction surgery.¹⁵ We therefore hypothesized that the use of rehabilitation for all subjects selected for airway bypass would be beneficial, inasmuch as their muscular reconditioning is improved by the program, and which in turn allows further improvement in their overall condition, enhancing the benefit received from reducing hyperinflation by the airway bypass procedure.

The air flow measurement FEV₁ has been used as a standard outcome measure in both the NETT¹⁰ and in bronchoscopic lung volume reduction⁸ studies. However, the lack of significant change in FEV₁ after airway bypass, in the presence of significantly improved dyspnea and RV reduction in this study, suggests the effect produced by airway bypass is not reflected in the rapid exhalation as measured by FEV₁, but in reduced gas trapping as measured by RV. Indeed, FEV₁ has not been found to correlate with patient-centered outcomes such as exercise tolerance, dyspnea, or health-related quality of life, as opposed to hyperinflation, which is directly associated with dyspnea and exercise limitation.¹⁶ Studies with short- and long-acting bronchodilators have shown that substantial reduction in

hyperinflation in patients with COPD may be followed by rather small changes in FEV₁.¹⁷ A recent study involving endobronchial valves for emphysema also has failed to demonstrate significant changes in FEV₁.¹⁸ The reduction in hyperinflation has been shown to correlate better with exercise endurance and dyspnea ratings than with spirometry parameters.¹⁹ The reduction of benefit observed between 1 and 6 months after the airway bypass procedure could be due to one or more factors, which include patient selection criteria, suboptimal selection of sites for stent placement, stent patency, or other yet-to-be-determined factors. Inasmuch as airway bypass relies primarily on abundant collateral ventilation, which is greatly enhanced in patients with severe emphysema, subjects with severely hyperinflated lungs are, theoretically, the most likely to benefit from the procedure. Retrospective analysis of our patients using RV/TLC ratios above and below median (Tables 2 and 3) suggests that the degree of pretreatment hyperinflation may be an important factor in indicating patients who are most likely to achieve long-term benefits. Analogous to other interventions for emphysema, the degree of chest remodeling and diaphragmatic motion can also play a role in the assessment of outcome, and studies are currently being carried out to investigate new methods. On the basis of these early results, we can anticipate that the target population for future studies and clinical application of this procedure will have to include patients with severe hyperinflation.

The ideal number and location of stents to place is yet to be determined. Initial attempts to implant approximately 10 stents were based on the study of excised human lungs.⁶ Analysis of the current data shows no correlation between the number of stents placed and the degree of improvement in RV at any time point. The ideal number and location of stent placement remains a focus of ongoing studies.

Analysis of the limited bronchoscopic evaluation at 6 months shows that paclitaxel-eluting stents seem to be associated with extended stent patency. These clinical results were consistent with the work reported by Choong and associates,¹⁴ which showed that 65% of paclitaxel-eluting stents in animals were patent at 12 weeks. Stent patency also remains a focus of ongoing studies. New approaches to mapping and computed tomographic evaluation of the stents may facilitate this work.

The major intraoperative risks involved in airway bypass include pneumothorax and airway bleeding. No instances of pneumothorax occurred and all but one bleeding episode was controlled locally with instillation of cold saline and epinephrine solution. The major bleeding episode that resulted in the subject's death was attributable to stent placement away from the original "quiet spot" identified by the Doppler probe. An extensive investigation conducted by the study's Data and Safety Monitoring Board, including a video review of the procedure regarding this event, resulted in several recom-

mentations. Modifications incorporated into the study included a stand-by balloon blocker placed into the main bronchus during every procedure and the repeat Doppler scanning of the passages created and dilated by the needle-balloon device before deploying the stent.

The present study was designed to demonstrate the applicability of airway bypass to a multicenter study and proof of concept of the airway bypass procedure using the paclitaxel-eluting stent in subjects with moderate-to-severe emphysema. The subjects in this study had more severe disease (greater RV and TLC, shorter 6MW, less quality of life, and a higher percentage of homogeneous emphysema, 94% vs 46%, respectively) than those in the NETT. By retrospective analysis, the most statistically significant results were observed in patients with the greatest degree of pretreatment hyperinflation.

In conclusion, early results of the airway bypass procedure using a paclitaxel-eluting stent in a multicenter study have been shown to reduce hyperinflation and dyspnea and to improve pulmonary function in subjects with severe emphysema, especially in those with severe hyperinflation. The clinical improvements demonstrated in these preliminary clinical results support further investigation of the airway bypass procedure. Questions about patient selection, the optimal placement of the stents, and stent patency provide direction for further study.

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Discussion

Dr Cliff K. Choong (Cambridge, United Kingdom). Dr Cardoso, congratulations to you and your co-investigators on this study and results. I am glad to see that the good feasibility and safety results that were found in the animal studies that we had performed have been largely translated and reproduced by you and your clinical investigators in this multicenter study. In the animal study that we had performed at Washington University, we had found that 65% of paclitaxel stents were patent at 18 weeks whereas the control stents were all occluded at 4 weeks. This information was presented in 2005 before this Association and published in the January 2006 issue of the *Journal of Thoracic and Cardiovascular Surgery*. I have always been curious about patency in clinical studies on patients. On the one hand, it may be that ventilation through the airway bypass stents between the airway and the destroyed emphysematous lungs may improve the patency rate, but on the other hand, thick mucus and infection in patients with COPD may accelerate occlusions of the airway bypass stents. Did you and your investigators assess the patency of the airway bypass stents in your patients? If you did, what were the percentage of patency and the duration of patency, and how did that correlate with the clinical findings?

Second, have you any idea as to what may be the optimal number of stents for treating patients with homogenous emphysema?

The last issue concerns collateral ventilation. It seems to me that the 1-way valve such as those produced by Emphasys and Spiration may be useful in patients with minimal or no collateral ventilation and causing atelectasis of the segments or lobes in those areas, whereas the airway bypass stents may be effective and useful in patients with extensive collateral ventilation. I think there

may be a role in combining both modalities. I would appreciate your opinion on that.

Dr Cardoso. Thank you very much, Dr Choong, and thanks for the major contribution you have made. You paved the ground for this clinical study to be done today with your animal data.

Regarding the number of stents, we participated in three different arms of this protocol, and this is the last arm. At the beginning, the idea was to insert as many stents as possible. In a few patients in whom we could not insert many stents owing to anatomic reasons or for the presence of vessels around the airway, we realized that these patients did as well as the patients who had received many stents. We then concluded that perhaps it is not necessary to use too many stents to get results. It became clear that what is really necessary is to deflate both lungs.

Regarding patency, unfortunately I cannot provide this information right now because this study is still ongoing. We will have the data on patency when the study is completed in a few months. What I have is anecdotal data on the last 2 patients on whom we did the 6-month follow-up—the last 2 patients we treated in this protocol. One of them had the stents completely open, whereas the other patient had all the stents closed. We are still trying to figure out which factors play a role in stent patency.

Regarding collateral ventilation and its effects, these are different things. The valve system and the stents work in different emphysema patients. If we are talking about homogenous emphysema with very severe destruction in the parenchyma, then these are probably not the best patients for the valves but for the stents. Since emphysema is generally a very heterogeneous population, those patients who do have destruction, for example, in the upper lobes with target areas could be treated with valves in the upper lobes and the rest of the parenchyma could be treated with stents. Time will tell about the outcome.

Dr Erino Rendina (*Rome, Italy*). Again, congratulations, Dr Cardoso, on an excellent presentation. These are, to the best of my knowledge, the first clinical results published on airway bypass. You are to be congratulated on being able to demonstrate benefits to this procedure at intervals as long as 6 months. I would like to

ask your opinion on two issues. The first issue is the selection process. I did not see in your presentation anything about the evaluation of the small airway in these patients. I think the status of the small airway is a very important issue because it has a relation with the destructive component of emphysema. Would you like to comment on that?

The other issue is the deaths that occurred among your patients. That stresses an important point. The airway bypass is a surgical procedure. In our early experience with airway bypass at the time when the stents were not available, we also had an episode of bleeding, but we were able as surgeons to control this very serious occurrence, and the patient had no problems. I think it is important to keep in mind that, though safe, this remains a surgical procedure that should be performed by surgeons.

Dr Cardoso. Thank you very much. Dr Rendina is another cornerstone of this procedure.

Regarding selection, patients who have severe bronchitis probably are not the best candidates. As a matter of fact, we had 1 patient whose airway was so severely deranged because of bronchitis that we could not insert any stents. Furthermore, distal airway disease is something that could eventually alter this mechanism by which airway bypass works, which is ultimately dependent on the enhancement of collateral ventilation. I think one must be very selective to get good results.

Regarding expertise, I think surgeons and pulmonologists who can treat massive hemoptysis can do this procedure. That is not an issue. The issue is that this has to be done in a surgical environment with all the equipment needed because it is an invasive procedure and must be done by people who are very familiar with interventional endoscopy. The regular diagnostic endoscopist probably needs a lot of training to do this procedure safely. Nonetheless, it is a rather straightforward and very safe procedure.

Dr John D. Puskas (*Atlanta, Ga*). Thank you, Dr Cardoso, for your landmark study and congratulations on demonstrating for the first time in a clinical trial the benefit of endoscopic airway stenting.