A multicenter trial of an intrabronchial valve for treatment of severe emphysema

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The members of the Spiration research group are listed in Appendix 1.

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Objectives: Minimally invasive endoscopic treatment of emphysema could provide palliation with less risk than lung volume reduction surgery and offer therapy to patients currently not considered for lung volume reduction surgery. The Intrabronchial Valve is used to block bronchial airflow in the most emphysematous areas of lung.

Methods: Patients with severe chronic obstructive pulmonary disease and heterogeneous upper lobe–predominant emphysema were eligible. Patients underwent flexible bronchoscopic placement of valves into segmental or subsegmental airways in both upper lobes. Outcomes assessed over a minimum of 6 months of follow-up included the safety, feasibility, tolerance, and success of valve placement; health-related quality of life; exercise capacity; pulmonary function; and gas exchange.

Results: Five centers treated 30 patients. Patient follow-up ranged from 1 to 12 months. A mean of 6.1 valves were placed per patient. Valves were positioned by means of flexible bronchoscopy in 99% of desired airways, and the procedure duration ranged from 15 to 125 minutes (mean, 65 minutes). Hospital discharge occurred within 2 days in 27 of 30 patients. There were no deaths or episodes of valve migration, tissue erosion, or significant bleeding. Eighty-three percent of patients had no adverse events judged probably or definitely related to the device. Patients experienced significant improvement in health-related quality of life, although the physiologic and exercise outcomes did not show statistically significant improvements.

Conclusions: These first multicenter results with the Intrabronchial Valve demonstrate significant improvements in health-related quality of life and acceptable safety, ease of use, and procedural complication rates. The valve might be a safer and less-invasive alternative to surgical therapy for patients with severe emphysema.

Emphysema affects 2 to 3 million persons in the United States and is characterized by progressive deterioration in pulmonary function, with exercise limitation, disabling dyspnea, and an inexorable decrease in quality of life. Until recently, surgical palliation of the symptoms of emphysema was only used for the very small subset of patients with giant bullae. Lung transplantation was introduced as an option for patients with end-stage emphysema in the 1980s, but it is only offered to the most severely ill patients who have minimal comorbidity and

Abbreviations and Acronyms

COPD = chronic obstructive pulmonary disease
 IBV = Intrabronchial Valve
 LVRS = lung volume reduction surgery
 NETT = National Emphysema Treatment Trial
 SGRQ = St George's Respiratory Questionnaire

younger age. The number of transplantations performed is further limited by a shortage of lung donors, with only approximately 400 patients with emphysema per year (0.013%) undergoing transplantation.¹ Lung volume reduction surgery (LVRS) was reintroduced in the early 1990s and has had its efficacy investigated more thoroughly than perhaps any other new surgical procedure. LVRS improves pulmonary function, exercise capacity, and quality of life in selected patients with severe chronic obstructive pulmonary disease (COPD) and emphysema, but it has demonstrated major limitations.² First, the benefit of LVRS is limited to narrow subsets of patients with certain patterns of emphysema and with minimal comorbidity.² Second, patients undergoing LVRS have significant risk of morbidity that can extend the period of convalescence before they can realize the desired clinical improvement or that might prevent benefit from LVRS at all.³

The goal for future developments in the treatment of advanced emphysema would be to provide similar benefit as LVRS, with less risk, shorter recovery, and decreased cost. Endobronchial occlusion with a plug or valve might be able to produce targeted areas of atelectasis and subsequent lung reduction with similar physiologic and functional outcomes to LVRS. Alternatively, valve occlusion of the airways might have effects that differ from LVRS, such as the ability to decrease dynamic hyperinflation, work of breathing, and dyspnea with exertion. The Intrabronchial Valve (IBV; Spiration, Inc, Redmond, Wash) is a novel implantable device designed as a one-way valve that is placed by means of flexible fiberoptic bronchoscopy. The IBV obstructs airflow into targeted bronchopulmonary segments and in unpublished animal model studies appears to allow drainage of distal air and mucus. This report describes the initial pilot human study results with the IBV to determine feasibility and safety data before proceeding to a larger pivotal clinical trial.

Materials and Methods

This prospective, open-enrollment, multicenter cohort study enrolled patients with heterogeneous, upper lobe–predominant emphysema, and severe COPD (Table E1). Patients excluded from the trial were those already accepted and listed for LVRS or lung transplantation, those defined as high risk within the National Emphysema Treatment Trial (NETT),⁴ those having a significant bronchospasm, or those with chronic bronchitis and heavy sputum

production. Screening studies were similar to those used by the NETT,⁵ including baseline physiologic, radiologic, and quality-of-life testing. Patients were required to fulfill a pulmonary rehabilitation program or complete more than 140 m in a 6-minute walk test. The clinical protocol was reviewed and approved by each investigating site's institutional review board and monitored by an oversight data safety monitoring board. All patients provided informed consent for the procedures, data collection, and participation in the clinical trial.

The IBV is an implantable device designed for placement in the segmental or subsegmental bronchi by means of flexible bronchoscopy (Figure E1). The valve is made of a nitinol framework. The valve's 5 distal anchors provide stability and allow distal seating of the valve into the airway without perforation. The proximal portion is made up of 6 support struts that are covered by a synthetic polyurethane polymer. The membrane-covered struts expand radially and form an umbrella shape that allows conformation and sealing to the airways with minimal pressure on the mucosa. The valve is designed to limit distal airflow, yet the membrane and support struts should allow air and mucus to flow out of the occluded segment by compressing the umbrella. The valve design includes a proximal center rod that allows early repositioning or removal.

Patients underwent general anesthesia with endotracheal intubation. Therapy generally consisted of bilateral occlusion of all upper lobe segments except for the lingula, with placement of valves into segmental airways, subsegmental airways, or both to occlude all planned segments. Airways were sequentially sized with a calibrated balloon to determine valve size. Available valve diameter sizes were 4, 5, 6, and 7 mm. For segments with a diameter of greater than 7 mm, subsegmental orifices were measured to define subsegmental valve size.

The IBV was deployed by means of flexible bronchoscopy with 2 different delivery systems. The direct-load system provided a loading kit that allowed the valve to be compressed and loaded retrograde into the 2-mm working channel of the bronchoscope (Figure E2, A). In the direct-load configuration the tip of the bronchoscope was inserted into the orifice to be occluded, and the tip of the scope was positioned at the desired depth of the valve anchors. The IBV deployment tool was used to advance the valve out of the working channel. When the anchor tips extruded and contacted the bronchial wall, the bronchoscope was withdrawn while continuing to deploy the valve until it was fully delivered out of the bronchoscope.

The catheter-load system compressed the valve into a 2.2-mm flexible delivery catheter with an integral deployment rod (Figure E2, B). The catheter was then placed through the working channel (≥ 2.6 mm) of the flexible bronchoscope and directed into the targeted airway. The valve was visualized through the clear sheath of the delivery catheter and positioned so that the top of the valve membrane and struts was at the level of the desired position in the airway. The valve was then deployed, the position was assessed, and adjustments were made as necessary. The catheter shaft was revised for the last 8 patients to prevent stretching and nondeployment of the valve. Before the catheter revision, the direct-load technique was the dominant method used.

Valves were deployed in all planned segments or subsegments, followed by a final visual inspection. The patient was then extu-

TABLE 1. Baseline and demographic data

	Mean $\pm$ SD	n	Range	Percent predicted (mean $\pm$ SD)
Age (y)	64 $\pm$ 10	30	42-78	
Male/female sex	19/11			
FEV ₁ (L)	0.86 $\pm$ 0.28	30	0.40-1.75	31.00 $\pm$ 9.40
FVC (L)	2.57 $\pm$ 0.79	30	1.34-4.44	70.40 $\pm$ 16.89
TLC (L)	7.74 $\pm$ 1.53	29	4.97-10.50	134.24 $\pm$ 24.18
RV (L)	5.10 $\pm$ 1.20	29	3.07-7.32	246.52 $\pm$ 60.30
D _l CO	10.50 $\pm$ 4.01	28	4.81-20.60	42.71 $\pm$ 13.02
PaO ₂	70.56 $\pm$ 8.37	28	53-84	—
Paco ₂	41.58 $\pm$ 5.47	30	29-55	—
6MWD (m)	334.06 $\pm$ 109.42	30	91-509	—
Work (W)	43.80 $\pm$ 24.76	28	1-116	—
SGRQ total scores	59.7 $\pm$ 13.7	29	32.3-86.6	—

SD, Standard deviation; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; D_lCO, diffusing capacity of lung for carbon monoxide; 6MWD, 6-minute walk distance; Work, maximum work on a cycle ergometer; SGRQ, St George's Respiratory Questionnaire.

bated and managed on a surgical/medical inpatient floor for standard postanesthesia COPD management, which included the use of bronchodilators and supplemental oxygen. Patients had a chest radiograph taken immediately after the procedure and each day of inpatient hospitalization. Prophylactic antibiotics and perioperative steroids were used at the discretion of the investigating physician. For the first 19 procedures, the protocol required hospitalization and observation for a minimum of 2 postprocedure days. Because patients typically had no obvious need for hospitalization on the second day after the procedure, the protocol-required stay in the hospital was decreased to a minimum of 1 postprocedure day.

Patients were asked to keep a symptom and medical history diary. The patients were evaluated at 1 to 2 weeks after discharge from the hospital with a history, physical examination, chest radiograph, and resting oxyhemoglobin saturation measurement. At 1 month after valve placement, patients had another follow-up visit and testing. The patients then underwent a second bronchoscopy procedure after either topical anesthesia with conscious sedation or general anesthesia was obtained. The implanted valves were inspected for evidence of tissue erosion, migration, and appropriate seal of the membrane against the airway wall and to assess for signs of complications, including purulence or granulation tissue. During this bronchoscopy, valves could be removed, removed and replaced, or added, as determined by the investigator. If new valves were inserted, the patient underwent general anesthesia, hospitalization, and follow-up similar to the initial procedure.

Patients returned for follow-up evaluation by the investigators at 3-, 6-, and 12-month intervals. Chest radiographs were analyzed at each visit to document the stability of the valve position. The investigators assessed intervening adverse clinical changes for their seriousness and any possible relationship to the device.

A panel of experts, investigators, and Spiration, Inc, personnel determined a priori adverse event definitions. A clinical events committee adjudicated all adverse events for severity and relationship to the device. The primary end point of the pilot study was safety, as measured by the incidence of migration, erosion, and/or infection related to the device. Other safety measures included

pneumothorax requiring a chest tube for more than 7 days, hospital length of stay beyond that required by the protocol, additional procedures required because of adverse events, COPD exacerbations, persistent cough, bronchitis or pneumonia, respiratory failure, hemoptysis requiring intervention, and death.

Three variables were identified prospectively as pilot study measures for efficacy: an increase in posttreatment forced expiratory volume in 1 second (FEV₁) of 15% or greater, an increase of 6-minute walk distance of 15% or greater, or an improvement in the St George's Respiratory Questionnaire (SGRQ) total score of more than 4 points. These thresholds for minimal clinically important differences were based on published literature.⁶⁻⁸ Other measures of efficacy included decrease in oxygen supplementation requirements, improvement in Medical Outcome Study Short-Form Health Survey (SF-36) scores, and improvement in the modified Medical Research Council dyspnea score. Dyspnea and general health-related quality of life were assessed with questionnaires that were provided onsite or through the mail. All questionnaires were completed during periods of clinical stability.

Descriptive data are expressed as means $\pm$ standard deviation, medians, and 95% confidence intervals. Categorical data are expressed as counts and proportions. Mean scores before and after valve placements were compared by using the Wilcoxon signed-rank test. A *P* value of less than .05 was considered statistically significant, and comparisons for multiple tests were not used. Spiration, Inc, assisted in data collection and collation and provided an independent consultant for statistical analysis.

Results

Thirty patients were treated at 5 clinical centers from January through July 2004 (Table 1). Patients had severe to very severe airflow obstruction, with air trapping, thoracic hyperinflation, and a reduced diffusing capacity of lung for carbon monoxide value. All patients had bilateral upper lobe treatment. The average initial procedure time was 65 $\pm$ 33 minutes (range, 15-125 minutes). The average time for the last 8 procedures (with the modified catheter) was 41

TABLE 2. Complications and thoracic events in the first 6 months

Periprocedure			Up to 30 d after valve implantation			30-180 d after valve implantation	
Bronchospasm	4*	6%*	COPD flare	4	6%	COPD flare	4
Arrhythmia, cardiovascular	6	9%	Bronchitis	3	4%	Bronchitis	4
Paco ₂ retained	2	3%†	Dyspnea	3	4%	Dyspnea	3
Dyspnea	1	1%	Thorax Pain	2	3%	Thorax Pain	1
Hemoptysis	1	1%	Hemoptysis	1	1%	Hemoptysis	1
			Pneumonia	4	6%‡		

See text for definitions. *COPD*, Chronic obstructive pulmonary disease. *Number of episodes and proportion of total procedures (n = 66). †Two episodes in 1 patient. ‡None in the area of Intrabronchial Valve treatment.

minutes. There were 184 valves in place at completion of the initial procedure and 194 valves after the completion of the 1-month bronchoscopy, for an average of 6.5 ± 1.6 valves (range, 5-10 valves) per patient. The airways treated were 166 (73%) segmental airways and 62 (27%) subsegmental airways. When 1 valve treated 2 segmental airways, it was counted as 2 segments treated. The 7-mm valves were used in 69% of the instances, with 6 mm at 27% and 5 mm at 4%, and only one 4-mm valve was placed. Successful valve placement was accomplished in all but 2 of the attempted sites (99%) at the first procedure, and all desired sites were treated after the second procedure. The 2 locations not initially treated were the anterior subsegments of the upper lobes of each lung, where the angle did not allow scope entry for direct-load placement. The 1-month bronchoscopy resulted in revisions in 17 patients with removal of 8 valves, replacement with 16 valves, and placement of 15 additional valves in new segments or subsegments. Reasons for valve revisions at 1 month were visual judgment that valves were angulated or too distal in an airway, resulting in incomplete contact between the membrane and an airway wall. Sometimes 1 segmental valve was removed and replaced with 2 subsegmental valves. In most cases valves were added for additional treatment.

All patients were extubated at the end of their procedure. The median hospital length of stay after the procedure was 2 days. The initial protocol required 2 days of postprocedure observation, which was later modified to only 1 day. Patients typically stayed in the hospital only for the protocol-required length of stay. However, 2 patients were discharged after 3 days. One patient remained hospitalized until transportation needs were addressed. One patient had a 33-day admission. After an uneventful procedure, the patient experienced chest pain, wheezing, and acute respiratory distress, which resulted in a cardiopulmonary arrest. The patient survived with a myocardial infarction. He later had a second arrest and experienced nosocomial pneumonia. All valves were removed 21 days after the original procedure. Follow-up 8 months after the initial valve placements showed a return to baseline, with no evidence of

adverse effects from valve implantation. One patient withdrew from the study before 6-month data collection because of the rigor of testing, and another withdrew at 8 months because of lack of response. Two patients withdrew at 7 and 9 months, respectively, for valve removal and anticipated LVRS.

Twenty-eight patients have been followed for at least 6 months after valve placement. Data are currently available on 6 patients at 12 months. Because the protocol and IBV design allows removal, 7 patients (48 valves) underwent late valve removal within the study period. Reasons for late valve removal were LVRS (2 patients) at 7 and 9 months, pneumonia in the area of valves (2 patients) at 9 and 12 months, and nonresponders who requested removal (3 patients) at 3, 5, and 8 months. Only 1 valve in a patient electing LVRS was not removed (1/48 [2%] valves) because of inadequate visualization and difficult access. Several more valves were difficult to visualize because of hyperplastic tissue, but these were removed with the aid of fluoroscopy.

On the basis of the judgment of the investigator and adjudication by the clinical events committee, no adverse events were definitely attributed to the valves. There were 6 events in 5 (17%) patients judged probably related and 20 events in 12 (40%) patients judged possibly related to the device. Fifty events were judged definitely not or probably not related. There were no unanticipated serious adverse events. Two patients experienced 5 anticipated serious adverse events, 3 events in the patient described above and pneumonia and a COPD exacerbation (at 22 and 53 days) that each required hospitalization in another patient. Specifically, valve erosion, migration, severe hemoptysis, and death did not occur. Device-, procedure-, or anesthesia-related events did occur in up to 9% of the procedures (Table 2). The most frequent event was cardiovascular, with a combination of arrhythmias, hypotension, or hypertension. Table 2 shows the occurrence of events on the procedure day and until discharge (periprocedure), after discharge and before 30 days, and from 30 days to 6 months after the initial procedure.

TABLE 3. Health-related quality-of-life, FEV₁, and 6MWD changes and proportion responding

SGRQ total scores	1 mo n = 27	3 mo n = 28	6 mo n = 23
Change compared with baseline, mean $\pm$ SD (<i>P</i> value)	−8.1 $\pm$ 9.6 (<.0001)	−6.9 $\pm$ 12.9 (.01)	−6.8 $\pm$ 14.3 (.05)
Proportion with change $\geq$ −4 points	17 (63%)	16 (57%)	12 (52%)
Proportion with change $\geq$ −8 points	11 (41%)	10 (36%)	9 (39%)
FEV ₁	n = 29	n = 28	n = 26
Proportion with change $\geq$ 15%	3 (10%)	5 (18%)	2 (8%)
6MWD	n = 28	n = 27	n = 25
Proportion with change $\geq$ 15%	8 (29%)	3 (11%)	6 (24%)

FEV₁, Forced expiratory volume in 1 second; 6MWD, 6-minute walk distance; SGRQ, St George's Respiratory Questionnaire; SD, standard deviation.

The only consistent evidence of efficacy was documented by the SGRQ. There were significant changes in the SGRQ scores at all postprocedure time points compared with the preprocedure baseline (Table 3). The mean change at 6 months was -6.8 ± 14.3 points. Fifty-two percent of the patients had a clinically meaningful response (SGRQ score improved by at least -4 points) at 6 months after valve implantation. The NETT used a more stringent change (SGRQ score improved by greater than -8 points), and 39% of patients receiving LVRS in this trial met these criteria at 6 months. The other measures of efficacy before and after valve implantation are shown in Table E2. The only statistically significant changes occurred in health-related quality of life.

Discussion

The results of several large cohort studies and randomized trials have firmly established the benefit of LVRS for palliating symptoms in select patients with emphysema.^{2,3,9-14} However, LVRS has 2 major limitations that affect its applicability to many patients with emphysema. First, LVRS is indicated in only a fairly narrow subset of patients based on pattern of disease and several exclusionary comorbidities.² Second, LVRS is a major operative procedure for a high-risk patient population, with its attendant morbidity and mortality. Patients undergoing LVRS can anticipate a postoperative mortality of 5.5%, major pulmonary morbidity of 30%, and cardiac morbidity of 20%.³ Patients spend significant time recovering after LVRS, with nearly 30% of patients still hospitalized or in rehabilitation facilities 1 month postoperatively and 15% still not at home 2 months after the operation.² Attempts to minimize surgical morbidity from thoracotomy or median sternotomy with minimally invasive thoracoscopic LVRS have not shown any difference in the incidence or profile of complications.¹⁵

Within 3 to 4 years after the reintroduction of LVRS, several investigators proposed a variety of bronchoscopic techniques to treat patients with emphysema and COPD.¹⁶⁻²² Some of the pilot studies of segmental airway obstruction with 1-way endobronchial valves have been

able to show improvement in FEV₁, exercise capacity, or quality of life, although the patient numbers are small, and the results are variable. Endobronchial valve placement has been well tolerated, with complications of pneumothorax in 15% to 25% and few reports of bronchospasm or obstructive pneumonia. Reported in-hospital length of stay for the pilot endobronchial valve studies has been 6 to 10 days.¹⁹⁻²²

The IBV was designed as a 1-way valve to limit airflow into the distal bronchopulmonary segments in an effort to achieve lung volume reduction, reduction of dynamic hyperinflation, and other physiologic changes, with subsequent improved functioning, lessened dyspnea, and improved quality of life. The valve has been successfully removed in animal studies at periods ranging from a few days to 12 months.²³ This design benefit is important for initial safety and possible efficacy, allowing valves to be removed and repositioned for optimal effect and allowing valve removal for any early valve-related complications.

This pilot clinical trial is, to date, the largest published experience with bronchoscopic approaches to emphysema and the first with results beyond 3 months. Valve implantation was technically straightforward, with short procedure times even across multiple bronchoscopists and multiple clinical centers. In this initial clinical experience placement of valves was successful in all desired segments and sub-segments. Valves were able to be easily adjusted, removed, or replaced at the initial and follow-up procedures. Although intended as permanent implants, valves were able to be removed up to 12 months after implantation. Early and late reversibility of the procedure has not been previously addressed in the endobronchial lung reduction literature but has important implications in the event of adverse events related to the valve or an elective decision to remove the valves if there is an absence of clinical benefit.

This clinical trial had a protocol-driven hospital stay of 2 postprocedure days and, later, 1 postprocedure day. Most patients were hospitalized only because of protocol requirements, with a median hospital stay of 3 days (90%), comparing favorably with earlier series with hospital stays 2 to 3 times as long. There were very few hospital or 30-day

complications and no serious late valve-related complications, confirming a very high safety profile. Specifically, there were no instances of pneumothorax, obstructive pneumonia, intractable cough, or valve dislodgement in the first 6 months. Our clinical experience suggests that endobronchial treatment of emphysema with the valve can likely be performed as an outpatient procedure in the future because of the high degree of procedure safety and good patient tolerance. This is important from a public health and cost-effectiveness perspective. Surgical lung volume reduction, even in the most select subgroup with low exercise tolerance after rehabilitation and heterogeneous upper lobe disease, has an estimated cost of approximately \$100,000 per quality-adjusted life-year, with much of this cost a result of the initial hospitalization.²⁴

The current trial was not designed to establish effectiveness, although data were collected to provide guidance for the design of a larger randomized pivotal trial. In this study valve placement did not produce significant changes in FEV₁, lung volume, alveolar gas exchange, or exercise capacity. In contrast, significant improvements were found in disease-specific quality of life, as measured by the SGRQ. One possible explanation is that these patients achieved a placebo effect as a benefit of having an intervention in a clinical trial. However, placebo effects on the SGRQ within a pharmacology trial showed an improvement of only 4 points,²⁵ and experts have suggested that placebo effects diminish over time. The mean improvement at 1 month in this series was greater than 8 points, and this was sustained at 6 months, which is suggestive of a true treatment effect not captured by the common spirometry, lung volume, alveolar gas exchange, or exercise measures.

Although the original goal of endobronchial therapies has been to mimic surgical lung reduction by promoting atelectasis in treated segments, the achievement of this goal has been sporadic in previous reports and was noted only a few times in this study (data not shown). Although atelectasis is achieved in animal studies, this appears harder to achieve in the setting of collateral ventilation in patients with end-stage emphysema. There are several possible mechanisms of action that might explain the improvement of patients in our series. Valve placement in the more severe segments might help to redirect ventilation to better-perfused segments and improve ventilation-perfusion matching and symptoms without seeing an obvious spirometric or lung volume effect. The other mechanism of improvement can be seen only with exercise because of a possible treatment effect on dynamic hyperinflation.²⁶ During exercise, increased respiratory rate can lead to increased air trapping, particularly in areas with worse emphysema and high compliance, ultimately increasing lung volumes and worsening exercise tolerance and dyspnea. Endobronchial occlusion might help to mitigate dynamic hyperinfla-

tion during exercise and improve symptoms without showing improvements in resting pulmonary function.

The patient's primary motives for seeking palliative therapies for end-stage emphysema are to improve symptoms, functioning, and health-related quality of life.²⁷ This study showed overall improvement in disease-specific quality of life, whereas only a subset of patients showed improvement in lung function or exercise capacity. In addition to seeing improvements in health-related quality of life, investigators wish to see improvement in more objective measures, such as FEV₁ and exercise capacity, which might or might not function as surrogates for quality of life.²⁷ Two recent randomized controlled trials of LVRS have focused on a quality-of-life end point as a primary outcome.^{10,11} Targeted endobronchial occlusion of upper lobe segments in patients with emphysema can be achieved with very high success and low morbidity and might provide palliation of symptoms for some patients. Endobronchial therapies for emphysema can create treatment options for patients not currently considered candidates for LVRS and might offer less morbidity and more acceptability for LVRS candidates. Further studies need to concentrate on quality of life as the fundamental end point and try to establish the important mechanisms of improvement.

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Appendix 1

Spiration research group: Cedars-Sinai Medical Center, Los Angeles, Calif: R. McKenna, W. Houck, D. Kusuanco; Cleveland Clinic Foundation, Cleveland, Ohio: A. Mehta, T. Gildea, S. Murthy, Y. Meli; North Shore University Hospital-Long Island Jewish Health System, Manhasset, NY: D. Ost, A. Talwar, E.

Figueredo; University of Pennsylvania Medical Center, Philadelphia, Pa: D. Sterman, A. Musani, M. Machuzak, A. Haas, B. Finkel; University of Washington Medical Center, Seattle, Wash: D. Wood, M. Mulligan, K. Seymour.

Data Safety Monitoring Board: Gordon Snider (Chairman), Bartolome Celli, Jamie Stoller, and Satoshi Furukawa.

Clinical Events Committee: Roger D. Yusen (Chairman), Matthew Brenner, and Stephen D. Cassivi.

Discussion

Dr John D. Mitchell (Denver, Colo). Doug, I want to congratulate you and your coinvestigators on this very nice study, article, and presentation. Two of the biggest problems with surgical LVRS are the attendant morbidity and mortality associated with the procedure and the cost. One would hope that the development of less-invasive endobronchial therapies, such as this valve, could lead to expansion of the subgroup of patients with emphysema who might benefit from LVRS with less risk and at a lesser cost.

I just have a couple of questions for you. First, I wonder whether you could comment on some of the technical aspects of valve implantation. Is general anesthesia necessary? Are some segments and subsegments harder to instrument than others? And is this what led to considerable variation or range of the procedure times seen in the study?

Dr Wood. In terms of the first part of that question, general anesthetic is probably not necessary. We chose to use general anesthesia in this initial experience to decrease the possible technical difficulties and variability of doing this in an awake patient. All that said, I think that even later, as we gain experience, there still might be some benefit of doing it with a general anesthetic. There is a lot of airway manipulation of multiple segments, and it is very easy to do with a patient anesthetized. I think that the aspect of cough or respiratory movement might make some of those adjustments and placement of the valve more difficult. I do not have experience with that yet, but I can anticipate that that might be the case.

In terms of segments that are more difficult: yes, there are. As you get more acute angles into the anterior segments of both upper lobes, those can sometimes be difficult angles to achieve. Fortunately, the fact that we have a delivery catheter that goes through the flexible bronchoscope and can be visualized going into that segment does make it easier and that has become easier, for example, in the last 8 patients, as I describe. Still, sometimes the angles are difficult in the anterior segments.

Does that relate to the variability in procedure time? Possibly. I am not sure. I think that obviously this is an initial experience, and therefore the investigators as they were first doing this were completely new to the procedure, so that this involves all of the learning curve of doing the procedure as well, which I think we have gotten better at, but I think we would have to have substantially more experience to know whether we can decrease that time reliably.

Dr Mitchell. Second, were you surprised at the relative lack of complications caused by the valves? Specifically, I am interested in either valve migration or postobstructive pneumonia.

Could you comment on the hyperplastic tissue response that was seen associated with some of the valves several months after implantation?

Dr Wood. That is a good question. I am somewhat surprised. I expected first of all an instance of pneumothorax, which has been seen in similar trials of the Emphasis valve. They have had a significant incidence of pneumothorax, which we did not have in this initial phase A of our pilot trial, but I would have expected a big concern in plugging the airways of a patient with COPD as opposed to obstructive pneumonia. The valve is obviously purposely designed to allow mucus secretions to pass proximal to the valve, yet still it is functionally obstructed, and I would expect an instance of postobstructive pneumonia distal to these valves that, fortunately, we did not see. With additional time, we might.

In terms of the hyperplastic tissue, I have now removed valves in 2 of my patients out 1 year because they have not had a substantial improvement and now wanted to be considered for LVRS, and we wanted to remove the valves before that. They have had variable amounts of hyperplastic tissue obscuring the valves. Fortunately, we still have been able to remove all valves—100% of the ones that I have done even at 12 months—but some of them do have hyperplastic tissue proximal to the valve.

Dr Mitchell. Third, you were able to report that a substantial number of patients had a meaningful change in their health-related quality of life comparable with that seen in the NETT. When you did that comparison, did you use patients in the NETT with similar anatomic findings to those in your study?

Dr Wood. No, and it is not really possible to do that because that requires access to the primary data, which are not yet released for the NETT, to be able to try to stratify it to that degree. Therefore this is just a general NETT population.

Dr Mitchell. Finally, as I mentioned before, it would be nice if the use of these less-invasive technologies could expand the pool of patients with emphysema eligible for LVRS. In this study you limited your patient population to those who met generally the NETT criteria and had upper lobe–predominant disease, perhaps the group that you would expect to have the best outcome from this procedure. Could you comment or maybe speculate how this device might work in those with non–upper lobe disease, those deemed high risk by NETT criteria, perhaps even those with homogeneous disease and those with significant medical comorbidities?

Thank you very much. I enjoyed the article.

Dr Wood. Thank you, John. In terms of speculation and the reason for selecting this most favorable subset as an initial pilot series, you can probably understand the desire to do that when your initial study is a safety study looking at feasibility more than effectiveness. That is the reason for the stringent selection criteria in this phase. You are right that if in this phase it proves to be effective and a pivotal trial, then I think we should expand the indications and look at patients who otherwise might have contraindications to LVRS, as I introduced at the beginning of this, who might benefit from this or other forms of endobronchial therapy.

Dr Jerome McDonald (*Lakewood, Wash*). One of my concerns about this particular procedure over LVRS is that you have developed an obligate shunt, and I was wondering whether there is going to be any assessment in your future trials of efficacy with any perfusion studies or any way to assess whether an obligate shunt is going to decrease some of the effectiveness or efficacy of the procedure.

Dr Wood. In fact, most likely what has happened is the opposite of what you are talking about, which is an improvement in ventilation-perfusion match rather than a worsening. In fact, if you look at these patients, they have such low compliance in their upper lung fields that they are preferentially ventilated but very poorly perfused. Therefore, in fact, one of the ways that valves might be effective in improving patient quality of life is actually by improving ventilation-perfusion mismatch by decreasing the ventilation in an area that is already underperfused.

Dr Donald Low (*Seattle, Wash*). Doug, I enjoyed the article. I would specifically like to ask you a question regarding something that is in your abstract regarding follow-up bronchoscopy. It looks like that was a routine aspect of your ongoing assessment in these patients. I would like you to just let us know when this was done, and interestingly, I note that 17 patients—more than half of your patients—either had valve revision or additional valves placed. The valve revision issue is interesting considering how low your migration or other problems were. Could you tell us a little bit about what that valve revision was all about and what indicated the need for additional valves in selected patients on the follow-up bronchoscopy?

Dr Wood. Very astute of you, Don. I actually left that out because of lack of time, but in fact the protocol required a 1-month follow-up bronchoscopy that we wanted to do to assess valve placement and adequacy of seating of each of the valves and lack of migration, so that was a part of the planned protocol. All patients had a follow-up bronchoscopy at 1 month. Of the 30 patients, 17 of them had some revisions of their valves at that 1-month planned bronchoscopy. Some of them had valves removed. Some of them had valves removed and replaced, and some had additional valves placed. The most common rationale for each of them was not any valve migration but an appearance of a valve that looked like it might not be occlusive because of angulation or because of a wrinkle in the valve membrane that we thought could possibly be improved by a different size or better seating of the valves, and therefore those valves were removed and replaced. That was the most common indication. The reason for new valves being placed is sometimes that we were cautious in the initial placement and did not necessarily occlude every segment that we would like to and with more confidence would treat additional segments at the second bronchoscopy. Actually, after the second bronchoscopy, there were 10 more valves than the 184 that I presented in the article here.

Dr Henning Gaisert (*Boston, Mass*). I very much enjoyed your presentation, Doug. In other areas of the airway, when prosthetic devices are being placed, it is not necessarily clinical infection but colonization with particular organisms that indicate a higher risk of long-term infection, these organisms being particularly *Staphylococcus aureus* and *Pseudomonas* species. Have you done any culturing of the airway to see whether you get these specific organisms?

Dr Wood. No, we have not.

Dr Gaisert. Thank you. I very much enjoyed it.

Unidentified speaker. Nicely done, Doug. As to volume reduction surgery, one of the ways it works is it reduces the size of the lungs and mechanics improve and so on. Do you have any idea whether you are actually reducing the size of these lungs with these valves? Do you see it?

Dr Wood. The answer to that is, at least in this pilot experience with the first 30 patients, no. We are not reducing the size of the lungs, and that is kind of what my next-to-last slide was about. We have different mechanisms working here than mechanisms that we thought were going to be working when we try to duplicate LVRS. Clearly the patients are having an improvement in quality of life, but the objective measures that we have used in LVRS are not necessarily representing the reason that these patients are having an improvement. It might be things like dynamic hyperinflation. I will say just as a teaser that we have moved into a second phase of this study already and with a slightly different valve design and some more aggressive treatment, and in that group we are starting to see volume reduction as well with the atelectasis that we would kind of like to see. Surgically what we were thinking that we were aiming for is an atelectasis developing in the upper lobes to mimic the effects of LVRS, but at least in these first 30 patients, that was not seen to any reliable degree.

Dr Joseph Shrager (*Philadelphia, Pa*). Doug, how is it that these did not have surgical LVRS? In other words, did they have to be assessed by a surgeon or decline having surgical LVRS, given that you have a proved therapy and now have an experimental therapy?

Dr Wood. It is a good question. Some of these patients were not candidates for LVRS. For example, one of my patients had

a previous coronary artery bypass graft and was not a candidate for LVRS but would very much be a candidate for an endobronchial therapy. Other patients were candidates for either, and they were all in centers that could do LVRS, obviously in surgical centers like ours. They were all counseled about the choices of LVRS or involvement in this clinical trial. At the other centers, with the pulmonary physicians as principal investigators, there was the same counseling. The effort was to provide patients with counseling about all of their options, including surgical volume reduction.

Dr Shrager. The other issue is, can you speculate about why—you touched on this a little bit—the FEV₁ is not improved, whereas the quality of life is improved?

Dr Wood. Well, the FEV₁ surprisingly was not improved where quality of life was and that is where I think our dilemma is, except we know that FEV₁ is not a reliable surrogate for improvement after LVRS either, with a substantial number of patients having much more significant improvement in their functional capacity and quality of life that is not well represented by FEV₁. Our problem is that we are not yet very good at measuring the right measurement, and FEV₁ is common, so we use it a lot, but it is not a very reliable measure of efficacy in these types of treatments for emphysema.

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TABLE E1. Inclusion and exclusion criteria

Inclusion criteria

- Age ≥ 18 y
- Severe, heterogeneous, predominately upper lobe emphysema
- Ability to meet goals of a comprehensive pulmonary rehabilitation program
- 6-min walk of ≥ 140 m (459 ft)
- Can complete 3-min unloaded pedaling in exercise tolerance test
- PFTs
- $FEV_1 \leq 45\%$ of predicted value ($\geq 15\%$ of predicted value if age > 70 y)
- $TLC \geq 100\%$ of predicted value
- $RV \geq 150\%$ of predicted value
- Arterial blood gas
- $Paco_2 \leq 50$ mm Hg
- $Pao_2 \geq 45$ mm Hg on room air
- No coexisting medical problem that would preclude bronchoscopy
- If female with childbearing potential, negative pregnancy test result within 7 days before procedure
- Willing to undergo bronchoscopy and follow-up
- Ability to provide informed consent

Exclusion criteria

- $FEV_1 \leq 20\%$ of predicted value with $D_{LCO} \leq 20\%$ or homogeneous emphysema
- Active asthma, chronic bronchitis, or clinically significant bronchiectasis
- Smoking within 4 mo
- History of recurrent infections with clinically significant sputum production
- Giant bulla (greater than one-third volume of lung)
- Pulmonary arterial hypertension (peak systolic pulmonary artery pressure > 45 mm Hg)
- Requires > 6 L/min O_2 to keep $SpO_2 \geq 89\%$
- Significant comorbidity

PFTs, Pulmonary function tests; FEV_1 , forced expiratory volume in 1 second; TLC , total lung capacity; RV , residual volume; D_{LCO} , diffusing capacity of lung for carbon monoxide; SpO_2 , arterial oxygen saturation.

TABLE E2. Quality of life, lung function, gas exchange, and exercise tolerance before and after valve placement (mean $\pm$ SD)

	Baseline (n)	1 mo (n)	3 mo (n)	6 mo (n)
FEV_1 (L)	0.86 ± 0.28 (30)	0.87 ± 0.29 (29)	0.89 ± 0.31 (28)	0.83 ± 0.32 (26)
TLC (L)	7.74 ± 1.53 (29)	7.75 ± 1.47 (29)	7.94 ± 1.27 (28)	7.75 ± 1.27 (25)
RV (L)	5.10 ± 1.20 (29)	5.04 ± 1.16 (29)	5.28 ± 1.09 (28)	5.07 ± 0.88 (25)
D_{LCO} (mL min^{-1} mm Hg $^{-1}$)	10.50 ± 4.01 (28)	10.43 ± 4.20 (29)	10.96 ± 4.3 (28)	11.07 ± 4.29 (25)
Pao_2 (mm Hg)	70.6 ± 8.4 (28)	72.9 ± 9.0 (28)	72.1 ± 10.6 (27)	71.7 ± 10.4 (24)
$Paco_2$ (mm Hg)	41.6 ± 5.5 (30)	41.9 ± 6.5 (28)	42.0 ± 6.2 (27)	43.3 ± 7.4 (25)
Prescribed O_2 (L/min)	1.12 ± 1.6 (30)	0.98 ± 1.1 (28)	1.07 ± 1.3 (27)	0.88 ± 1.1 (25)
6MWD (m)	334 ± 110 (30)	329 ± 114 (28)	330 ± 125 (27)	360 ± 113 (25)
Exercise max (W)	43.8 ± 24.7 (28)	41.3 ± 22.4 (28)	40.6 ± 19.3 (26)	40.2 ± 23.2 (24)
MMRC	1.9 ± 1.0 (26)	2.0 ± 0.7 (27)	1.9 ± 1.0 (25)	1.9 ± 1.0 (23)
SF-36, physical composite score	32.9 ± 7.1 (28)	35.1 ± 8.1 (27)	33.5 ± 7.2 (28)	35.2 ± 8.9 (25)
SF-36, physical function	25.3 ± 18.6 (29)	31.9 ± 21.3 (27)	28.0 ± 17.8 (28)	33.2 ± 21.7 (25)
SGRQ total score	59.7 ± 13.7 (29)	52.7 ± 14.4 (27)	53.7 ± 13.0 (28)	54.8 ± 14.6 (23)

SD, Standard deviation; FEV_1 , forced expiratory volume in 1 second; TLC , total lung capacity; D_{LCO} , diffusing capacity of lung for carbon monoxide; 6MWD, 6-minute walk distance; MMRC, modified Medical Research Council dyspnea score; SF-36, Medical Outcome Study Short-Form Health Survey; SGRQ, St George's Respiratory Questionnaire.

Figure E1. A, Intrabronchial Valve appearance and nomenclature. B, Intrabronchial Valve in an airway, as viewed with a flexible bronchoscope.

Figure E2. A, Direct-load delivery. The compressed valve is loaded into the distal end of the working channel in the flexible bronchoscope and extruded with a specialized catheter when the bronchoscope is seated in the targeted airway. B, Catheter-load delivery. The valve is constrained within a flexible delivery catheter that is deployed through the working channel of the flexible bronchoscope.