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A Multicenter Pilot Study of a Bronchial Valve for the Treatment of Severe Emphysema

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For editorial comment see p. 191

Key Words

Bronchial valve · Bronchoscopic treatment of emphysema · Chronic obstructive pulmonary disease · Emphysema · Endobronchial lung volume reduction · Valve placement

Abstract

Background: Chronic obstructive pulmonary disease (COPD) affects millions of people and has limited treatment options. Surgical treatments for severe COPD with emphysema are effective for highly selected patients. A minimally invasive method for treating emphysema could decrease morbidity and increase acceptance by patients. ***Objective:*** To study the safety and effectiveness of the IBV® Valve for the treatment of severe emphysema. ***Methods:*** A multicenter study treated 91 patients with severe obstruction, hyperinflation and upper lobe (UL)-predominant emphysema with 609 bronchial valves placed bilaterally into ULs. ***Results:*** Valves were placed in desired airways with 99.7% technical success and no migration or erosion. There were no procedure-related deaths and 30-day morbidity and mortality were 5.5 and 1.1%, respectively. Pneumothorax was the most frequent serious device-related complication and primarily occurred when all segments of a lobe, especially the left UL, were occluded. Highly significant health-related quality of life (HRQL) improvement (–8.2 ± 16.2, mean ± SD change at 6 months) was observed. HRQL improvement was associated with a decreased volume (mean –294 ± 427 ml, $p = 0.007$) in the treated lobes without visible atelectasis. FEV_1, exercise tests, and total lung volume were not changed but there was a proportional shift, a redirection of inspired volume to the untreated lobes. Combined with perfusion scan changes, this suggests that there is improved ventilation and perfusion matching in non-UL lung parenchyma. ***Conclusion:*** Bronchial valve treatment of emphysema has multiple mechanisms of action and acceptable safety, and significantly improves quality of life for the majority of patients.

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Introduction

Chronic obstructive pulmonary disease (COPD) affects over 10 million people in the United States and 280 million in the world, with an estimated prevalence of 7–9% [1, 2]. In addition, patients underestimate the magnitude of their limitations and thus COPD remains largely underdiagnosed [2]. The airflow limitation of COPD is by definition only partially reversible, so using airflow improvement to assess a treatment response has led to undeserved nihilism regarding treatment [3].

Patients with COPD should be comprehensively evaluated in order to individualize therapy and determine the degree and pattern of their emphysema [4]. It is now known that smoking cessation, oxygen treatment, lung volume reduction surgery (LVRS), and noninvasive ventilation for severe exacerbations have a positive impact on mortality in COPD [3]. Surgical options for the treatment of emphysema – lung transplantation, bullectomy, and LVRS – are applicable to only a limited patient population. In fact, the National Emphysema Treatment Trial (NETT) evaluated 3,777 patients with severe COPD to enroll 1,218 patients for LVRS [5]. The NETT showed that LVRS significantly improves survival, in addition to quality of life and exercise capacity [6], but after exclusion of a high-risk group, LVRS was associated with a 5% postoperative mortality rate, and a 20 and 30% incidence of major pulmonary and cardiac morbidity, respectively [7]. For these reasons, LVRS is not being utilized to expected levels [8].

In attempt to achieve the physiologic benefits of LVRS with less morbidity and mortality, multiple minimally invasive investigative approaches for advanced emphysema have been initiated in the past decade. For heterogeneous emphysema, these approaches include bronchoscopic insertion of endobronchial blockers [9] or bronchial valves [10, 11] to promote absorption atelectasis and lung volume reduction, and injection of fibrin polymer into emphysematous lung parenchyma to induce tissue fibrosis with contraction of hyperinflated target lung zones [12]. Alternatively, for patients with homogeneous emphysema, another approach has been to reduce hyperinflation by creating stented transbronchial pathways between cartilaginous airways and emphysematous parenchyma [13]. None of these approaches have been approved in the United States for treatment of patients with advanced COPD.

The Spiration IBV® Valve is an umbrella-shaped bronchial valve that is placed via a plastic delivery catheter introduced through the working channel of a flexible bronchoscope. The IBV Valve System has US Food and Drug Administration (FDA) humanitarian device approval for use with selected prolonged postoperative air leaks [14] and has received market clearance in Europe through CE mark for the treatment of diseased and damaged lung. The valve limits airflow into targeted airways distal to the valve, but allows egress of trapped air and secretions. Previous publications described the preliminary data from the initial 30 patients enrolled in this pilot study [15], and part of the data have been published in summary form combined with an additional 7 patients treated at international sites [16]. Another publication has reported the quantitative computed tomography (QCT) results in the subset of patients with QCT [17]. We report here the final results from a pilot multicenter experience in the United States for bilateral treatment of severe heterogeneous upper-lobe (UL)-predominant emphysema.

Methods

Study Design

This study was a multicenter, prospective, open enrollment, consecutive case series for patients with severe emphysema, severe airflow obstruction, and hyperinflation (clinicaltrials.gov identifier NCT00145548). Patients were required to have heterogeneous, UL-predominant emphysema assessed by CT and lung perfusion scans. The specific inclusion and exclusion criteria for study enrollment have been published [15]. These criteria were similar to those used by the NETT, after exclusion of a NETT high-risk patient cohort (FEV_1 and DLCO <20% predicted). UL-predominant emphysema was determined by the visual comparison method (UL compared to non-UL) rather than by zonal scoring (heterogeneous compared to homogeneous) or CT density analyses [5]. Patients already accepted and listed for LVRS or lung transplantation were excluded. Patients with either a significant bronchospastic component to their emphysema, chronic bronchitis, or significant bronchiectasis were also not included. Patients had to complete or satisfy the goals of a pulmonary rehabilitation program. Baseline physiologic, radiologic, and quality of life measures were obtained before treatment and 1, 3, 6, and 12 months following valve placement. During the course of this pilot study, some revisions were made in the testing, testing methods, and treatment protocol. These changes occurred after patient numbers 30 and 58, so the changes and results are described as 1/3 and 2/3 intervals. The study protocol and all amendments were approved by the FDA, as well as by institutional review boards at individual centers. Patients provided informed consent to participate in all study-related procedures and data collection. Adverse events (AEs) were adjudicated by a clinical events committee and there was a data safety monitoring board.

Bronchial Valve and Procedure

The umbrella-shaped valve (IBV Valve; Spiration, Redmond, Wash., USA) is a self-expanding device with a nickel-titanium (Nitinol) frame. The 5 distal anchors secure the valve with lim-

ited airway penetration while the 6 proximal struts hold the membrane against the airway wall. The valve is easily compressed to expand and contract with breathing and allow proximal air and secretion flow. This ease of compression also results in gentle pressure on the mucosa. A central rod facilitates grasping with forceps for removal if necessary.

Two delivery systems, 'direct load' and 'catheter,' were developed for use and have been described [15]. In the catheter system, the valve was compressed into a catheter which can pass through a ≥2.6-mm channel in a flexible bronchoscope for placement into the desired bronchi. With catheter delivery the valve is positioned at the desired location and then the valve is unsheathed. The catheter method was preferred and was the only method used in the last third of the patients enrolled. Multiple valve sizes were available for different-size airways; 5-, 6-, and 7-mm diameter (uncompressed) valves were used throughout the trial. Four-mm valves were available early in the study and 9-mm valves were available late in the study. Airways were sized with a calibrated balloon catheter using standardized visual assessment.

Bronchoscopy was performed through an endotracheal tube or a rigid bronchoscope with local anesthesia and sedation or general anesthesia. Bilateral UL bronchial valve placement has been described previously (see online supplementary videos, www.karger.com/doi/10.1159/000259318) [15]. Given that enrolled patients had UL-predominant emphysema, both ULs were treated. Midway through the trial, adding treatment of the lingular segments of the left UL was allowed at the discretion of the investigator. Treatment of the lingular segments was again excluded for the last third of the trial. No segments in the middle or lower lobes were treated. After valve placement and visual inspection, patients were extubated and moved to the recovery area. In-hospital observation was required for a minimum of 2 nights at the initiation of the study, but then was changed to 1 night. Standard outpatient COPD medical regimens and management were continued during the study. Chest radiography was performed immediately following the procedure and on each day of hospitalization to confirm proper valve position and to assess for focal atelectasis, pneumothorax, and postoperative infiltrates.

Follow-Up

After leaving the hospital, patients were asked to keep a medical diary and record of any symptoms or changes in medical condition. The patients were evaluated within 1–2 weeks with chest radiography, resting oxyhemoglobin saturation, and history and physical examination. One month after the procedure, patients returned for an office visit with scheduled testing. During the initial 2/3 of the trial, a second bronchoscopy was required to inspect the valves and to allow added valve treatment as per investigator discretion. The added bronchoscopies were found to be of no additional clinical benefit, and were discontinued. Patients returned at 3, 6, and 12 months for outpatient visits with testing including a chest radiograph to ensure valve position, as well as a thorough follow-up medical history to assess for interval AEs.

Outcome Measures

In this pilot study, the primary outcome measure was safety, evaluated as the rate of observed migration, erosion, or infection associated with the IBV Valve during the first 3 months after placement. Other protocol-defined safety measures included COPD exacerbations, pneumothorax requiring chest tube for >7 days, hospital length of stay beyond protocol-allowed 3 days, persistent cough, bronchitis or pneumonia, respiratory failure requiring mechanical ventilation >24 h, hemoptysis requiring intervention, and death.

The secondary endpoint was an estimate of effectiveness. Three variables were used as pilot study efficacy measures: (1) 15% increase in FEV_1; (2) 15% increase in 6-min walk distance (6MWT), and (3) improvement in 4 points on the St. George's Respiratory Questionnaire (SGRQ). Other predetermined potential 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. Questionnaires were completed during periods of clinical stability as much as possible.

Quality of Life

Health-related qualify of life (HRQL) was measured with standardized and validated questionnaires. The SGRQ 2.1-English USA version was used for disease-specific measurement and the SF-36 V2™ Health Survey for general health. These questionnaires were selected because of scientific acceptance and widespread use, and to allow comparison to other therapy. The SGRQ, assessed over a period of 4–12 months, has 3 components – activity, impact, and symptoms – and includes questions about breathlessness, cough, and sputum. The score range is from 0 to 100, with higher scores indicating worsening health status. The SF-36 has questions about general health with a 4-week recollection period, and has 8 scales and 2 summary measures: physical and mental health. The administration and scoring of both was done following instructions and manual guides.

Pulmonary Function Testing and Exercise Testing

Pulmonary function testing was done in accordance with American Thoracic Society/European Respiratory Society guidelines and included spirometry before/after bronchodilators, lung volumes by body plethysmography, and a diffusion study. In addition, a metronome-paced breathing test was added during the last third of the study as a simple measure of dynamic hyperinflation [18]. A pacing rate of 30 breaths/min was used without controlling inspiratory or expiratory times.

Exercise testing included testing of walking and cycle ergometry. The 6MWT distances were measured at baseline and at follow-up visits in accordance with American Thoracic Society guidelines. When supplemental oxygen was needed, the flow rate was titrated at each test, as done in the NETT for the first 2/3 of the pilot study [19]. For the last third of the trial, the flow rate was initially determined by titration and held constant for follow-up testing.

Cycle ergometry was initially performed with the NETT method of determining maximum watts using supplemental oxygen in all patients [19]. During the last third of the trial, oxygen was used if prescribed for exercise and an initial test was performed to determine maximum exercise. Then constant load testing at 65% of maximum was repeated 2 or 3 times to establish a baseline value and was used for follow-up testing. It was planned to measure sequential inspiratory capacity values during cycle testing, but this additional testing was beyond the capabilities of the patients and technicians at the clinical laboratories and was not pursued.

Table 1. Baseline data

	Means ± SD	n	Percent predicted (means ± SD)
FEV_1, liters	0.87 ± 0.25	91	30.64 ± 7.85
FVC, liters	2.74 ± 0.81	91	74.38 ± 14.84
TLC, liters	7.57 ± 1.42	90	129.19 ± 18.3
RV, liters	4.74 ± 1.06	90	221.47 ± 49.35
DLCO	9.54 ± 3.45	89	38.57 ± 11.94
PaO_2	68.29 ± 9.05	89	–
$PaCO_2$	40.45 ± 4.96	91	–
6MWD, feet	1,108 ± 313	91	–
Max. work, W	41.28 ± 23.08	52	–
SF-36 PF	27.50 ± 17.13	90	–
SF-36 PCS	33.15 ± 6.17	88	–
SGRQ: total score	57.27 ± 12.71	88	–

n = Number of patients; PF = physical function; PCS = physical component summary.

Lung Perfusion Scans

Radionuclide scans of the lungs were obtained at baseline and 1–3 months after valve placement to confirm UL predominance and for targeting of treatment locations. The perfusion ratio in the upper regions of the lungs to that in the lower regions was quantified. To determine the ratio, each lung is divided into three zones, and a percentage of total perfusion is assigned to each zone. The ratio is calculated as the sum of the percentages assigned to the two upper zones divided by the sum of the percentages assigned to the four middle and lower zones [5].

Quantitative Computer Tomography

Details about QCT, the methods used, and results have been published [17]. In brief, at the start of the trial, CT imaging was performed at baseline to determine eligibility and consider treatment locations. A second CT was obtained after 1 month and before the second bronchoscopy to provide additional information for treatment planning. To determine the volumes of treated and untreated lobes with QCT, these existing CT scans were obtained when possible and then subsequent scans were done with methodology conducive to QCT measurements. The protocol was revised for the last third of the trial to add CT scans at 6 months when possible for already enrolled patients and to prospectively perform CT scans at baseline and 3 months for new patients.

QCT analyses were performed at the University of British Columbia with customized software (EmphylxJ). Each lung was manually segmented by determining the fissures separating the UL. The UL volume was subtracted from the total lung volume for the non-UL volume. All QCT volumes presented are the combined densities for the total volume.

Statistics

Descriptive data are expressed as means ± SD or medians. Categorical data are expressed as counts and proportions. Mean scores before and after valve placements were compared using Wilcoxon signed rank test. $p < 0.05$ was considered statistically significant, and adjustment for multiple tests was not performed. Device-related AEs are those considered definitely or probably device-related unless otherwise specified. Spiration (Inc.) assisted in data collection and collation and provided an independent consultant for statistical analysis.

Table 2. Patient enrollment and accountability at valve placement and months 1–12 (M1–M12)

	Patients, n				
	placement	M1	M3	M6	M12
Intent-to-treat	91	91	91	91	91
Deaths[1]	0	2	3	4	6
Withdrawal[1]	0	3	4	7	26
Expected patients	91	86	84	80	59
Actual patients	91	83	81	75	59
Follow-up, %	100	97	96	94	100

[1] These values are cumulative across time.

Results

Enrollment and Baseline Characteristics

This trial enrolled a total of 91 patients at 11 sites in the United States between January 2004 and August 2006. There were a slightly greater proportion of males than females (56 vs. 44%), and the mean age was 64.9 years (SD 8.2, range 42–79 years). Baseline physiological and HRQL characteristics for the overall patient population are summarized in table 1.

Patient Accountability

All patients enrolled underwent bronchoscopic placement of IBV Valves on study day 0 (operative day). No patients were lost to follow-up and accountability is shown in table 2. The expected follow-up ranged between 94 and 100% for the 4 visits. During the 12-month study, there were 7 patient withdrawals within 6 months and 19 more by 12 months. Except for 1 patient that withdrew consent and 1 that relocated, the withdrawals within 6 months were associated with an AE. In contrast, the withdrawals after 6 months were primarily in patients that had not felt improvement, except for 5 patients who withdrew because of an AE. Two withdrawals were after a diagnosis of lung cancer. The 3 deaths associated with pneumothorax are discussed below and the other 3 deaths

Table 3. Health status changes and proportion responding

	1 month	3 months	6 months	12 months
SGRQ total scores	(n = 80)	(n = 78)	(n = 67)	(n = 53)
Change compared to baseline	–5.2 ± 12.3 (p = 0.001)	–5.1 ± 15.2 (p = 0.011)	–8.2 ± 16.2 (p = 0.001)	–9.5 ± 14.4 (p < 0.001)
Proportion with changes ≤–4 points, %	51.3	52.6	55.2	56.6
SF-36 physical function	(n = 81)	(n = 79)	(n = 70)	(n = 54)
Change compared to baseline	3.4 ± 17.7 (p = 0.080)	3.2 ± 19.0 (p = 0.215)	7.1 ± 19.1 (p = 0.003)	8.0 ± 22.5 (p = 0.013)
Proportion with changes ≥10 points, %	35.8	35.4	42.9	48.1

were from sudden cardiac death, disease progression, and a non-study procedure complication.

Procedural Results

The mean bronchoscopy (not including preparation or anesthesia) time was 58.9 min (±31.0, range 15–187). The airways treated included 482 segmental airways (75%) and 157 subsegmental airways (25%). When a single valve was used to treat 2 segments, it was counted as 2 segments treated. There were 3 instances where a 9-mm valve was used to treat 3 segments (once the right UL), and twice to treat all 5 segments of the left UL. Target locations were successfully treated with valves in 609 of 611 airways (99.7% success), except for the left UL apical segment in 2 patients.

Patients were typically discharged from the hospital on the day after treatment. The median length of stay was 1 day. The mean length of hospital stay was 2.45 days, with a range of 1–33 days (SD 4.72).

A total of 609 valves were implanted in the 91 patients during the treatment phase. Valves were provided in 5 sizes: the 7-mm size was used for 55% (335 valves), the 6-mm for 26.8%, the 9-mm for 13.6%, and the 5-mm size for 4.4% of valve placements. Only one 4-mm valve was implanted throughout the entire pilot study.

A mean of 6.7 valves and median of 6 valves per patient were in place at the completion of treatment procedures (range 3–11 valves). All devices were identified by chest radiography throughout the 12-month study.

Bilateral UL airways were treated in 88 patients. Three patients had unilateral treatment allowed because there was preexisting disease with volume loss in the contralateral UL. Additional treatment of the 2 segments of the lingula of the left UL, in addition to the remainder of the left UL, was performed in 17 patients. The direct load system was used for 17.9% (109/609) of the implants. The catheter system was used for 82.1% (500/609) of the implants.

Health-Related Quality of Life Measures

The HRQL data show strong, significant, and durable improvements in both general and disease-related quality of life associated with IBV Valve treatment (table 3) with the mean changes in SGRQ, the proportion of patients with at least a 4-point improvement in SGRQ, and in the proportion of patients with at least a 10-point change in SF-36 physical function. A clinically significant gain in SGRQ was seen in 51% of the patients at 1 month. This responder rate increased to 53% at 3 months, 55% at 6 months, and 57% at 12 months. At all times the SGRQ changes were statistically significant along with significant improvements in physical function as assessed by the SF-36 at 6 and 12 months.

Regional Lung Volume Changes Measured by QCT

The impact of treatment on regional lung volume measured by QCT scans are detailed in table 4 (volume changes compared to baseline) and table 5. UL treatment resulted in a significant decrease in lung volume, almost 300 ml, at each time point; in 87% of the patients lung volume was decreased at 6 months. In addition, 75% of the patients experienced an increase in non-UL volume at 1 month; 84% demonstrated this gain at 3 months and 93% at 6 months. These volume changes are highly correlated (Spearman's –0.473, p = 0.002). In addition, using a definition for a QCT response of ≥10% increase in non-UL volume with any decrease in UL volume, there is a significant correlation between QCT response and HRQL response ($p < 0.01$) [17].

Regional Perfusion Measured by Lung Perfusion Scans

The lung perfusion scans showed a baseline decrease in upper-zone perfusion, and after bronchial valve placement there was a further reduction in UL perfusion indicating a shift to the lower zones. At baseline, the mean ±

Table 4. Regional volume changes and proportion changing

	1 month after treatment	3 months after treatment	6 months after treatment
UL volume	(n = 32)	(n = 32)	(n = 15)
Change compared to baseline, ml	–260 ± 407 (p < 0.001)	–269 ± 378 (p < 0.001)	–294 ± 427 (p = 0.007)
Patients with decreases in volume, %	81.3%	81.3%	86.7%
Non-UL volume	(n = 32)	(n = 32)	(n = 15)
Change compared to baseline, ml	259 ± 428 (p = 0.001)	248 ± 326 (p < 0.001)	375 ± 400 (p = 0.001)
Patients with increases in volume, %	75.0%	84.4%	93.3%

Table 5. Lung function, gas exchange, exercise tolerance, dyspnea, and health status before and after valve placement

	Baseline	1 month	3 months	6 months	12 months
FEV_1, liters	0.87 ± 0.25 (91)	0.85 ± 0.25 (83)	0.83 ± 0.26 (79)	0.83 ± 0.29 (71)	0.85 ± 0.33 (53)
TLC, liters	7.57 ± 1.42 (90)	7.53 ± 1.47 (83)	7.66 ± 1.47 (79)	7.58 ± 1.47 (70)	7.53 ± 1.62 (52)
RV, liters	4.74 ± 1.06 (90)	4.77 ± 1.12 (83)	5.00 ± 1.16 (79)	4.89 ± 1.17 (70)	4.71 ± 1.27 (52)
DLCO	9.54 ± 3.45 (89)	9.81 ± 3.66 (82)	9.57 ± 3.60 (79)	9.60 ± 3.51 (70)	9.43 ± 3.14 (51)
Pa_{O_2}	68.29 ± 9.05 (89)	68.27 ± 9.85 (81)	68.84 ± 10.40 (75)	68.92 ± 10.83 (63)	68.84 ± 11.23 (48)
Pa_{CO_2}	40.45 ± 4.96 (91)	40.58 ± 5.69 (81)	41.44 ± 5.43 (75)	41.82 ± 6.36 (64)	41.25 ± 6.10 (48)
Prescribed O_2, l/min	1.08 ± 1.34 (91)	1.21 ± 1.22 (82)	1.12 ± 1.29 (78)	1.01 ± 1.15 (71)	0.83 ± 1.11 (54)
6MWD, feet	1,108 ± 313 (91)	1,102 ± 323 (80)	1,112 ± 335 (76)	1,151 ± 335 (69)	1,173 ± 303 (49)
Work[1], W	39 ± 20 (77)	37 ± 24 (51)	41 ± 22 (43)	40 ± 23 (42)	40 ± 23 (29)
QCT UL, ml	3,379 ± 871 (61)	3,121 ± 827 (32)	3,216 ± 984 (32)	3,035 ± 1254 (15)	ND
QCT non-UL, ml	3,414 ± 824 (61)	3,696 ± 860 (32)	3,692 ± 975 (32)	3,475 ± 1019 (15)	ND
MMRC	2.0 ± 0.8 (87)	1.9 ± 0.8 (81)	1.8 ± 0.9 (79)	1.8 ± 1.0 (70)	1.6 ± 0.9 (54)
SF-36 PCS	33.15 ± 6.17 (88)	33.80 ± 7.87 (81)	33.49 ± 9.03 (79)	35.00 ± 9.77 (70)	35.37 ± 9.19 (54)
SF-36 PF	27.5 ± 17.13 (90)	30.94 ± 19.93 (81)	30.44 ± 21.59 (79)	33.88 ± 23.94 (70)	36.63 ± 23.97 (54)
SGRQ: total	57.27 ± 12.71 (88)	52.90 ± 13.67 (81)	53.06 ± 16.56 (79)	50.05 ± 18.00 (68)	48.53 ± 16.22 (54)
SGRQ: activity	78.60 ± 13.95 (88)	74.36 ± 17.24 (81)	73.91 ± 19.99 (79)	71.41 ± 22.20 (69)	69.43 ± 21.64 (54)
SGRQ: impact	42.92 ± 15.71 (89)	37.09 ± 15.10 (81)	38.66 ± 18.28 (79)	34.99 ± 18.01 (70)	33.91 ± 17.06 (54)
SGRQ: symptom	63.64 ± 17.45 (89)	64.43 ± 18.88 (81)	60.82 ± 20.36 (79)	57.92 ± 21.43 (69)	56.96 ± 20.69 (54)

Means ± SD (n of patients). MMRC = Modified Medical Research Council; PCS = physical component summary; PF = physical function.

[1] The follow-up values are for the patients that did maximum exercise testing throughout the study period.

SD perfusion ratio was 0.26 ± 0.20 (n = 91), compared to 0.20 ± 0.14 (n = 60) and 0.13 ± 0.07 (n = 25) at 1 and 3 months, respectively. Compared to the baseline value, the UL percent perfusion decreases were 6 and 9% further at 1 and 3 months, respectively.

Pulmonary Function, Arterial Blood Gas, Oxygen Use, Exercise, Questionnaire, and Breathing Test Results

The results of pulmonary function, arterial blood gas (ABG), oxygen use, exercise tests, and HRQL questionnaires are shown in table 5. In contrast to the significant and sustained improvements in health status and regional lung volumes, there were no significant and sustained changes in lung volumes, airflow rates, oxygen use, or ABG at rest. There was an increase of 43 feet (4%) in the mean 6MWT distance between baseline and 6 months after treatment, but this is not statistically significant, and the mean change per patient was 16 ± 227 feet (p = 0.19).

Cycle ergometry testing did not show improvement in maximum work by cycle ergometry. Likewise, the duration of exercise at a fixed workload was not consistently improved and was –62 ± 252 s (n = 19) at 3 months, –31

Table 6. Other protocol-defined safety measures (number of device-related occurrences in 91 patients)

Time after procedure	Months		
	<1	1–6	6–12
Pneumothorax (and air leak >7 days)	5	1	0
COPD exacerbation	0	1	1
Cough	1	0	0
Bronchitis or pneumonia in the post-treatment period	2[1]	N/A	N/A
Respiratory failure with mechanical ventilation >24 h	0	0	0
Bleeding and hemoptysis that requires hospitalization or transfusion	0	0	0
Death	1	1	0

[1] Bronchitis.

± 349 s (n = 14) and +88 ± 366 s (n = 4) at 12 months. Ergometry testing was difficult for these patients and many refused the testing at follow-up. The paced breathing testing results did not show significant changes in the inspiratory capacities at rest or after metronome pacing in the 27 patients tested (data not shown).

Safety Results

Primary Outcome

For the primary outcome measure of the study, there were no occurrences of IBV Valve migration or erosion in any study patient within the entire study period of 12 months. There was one episode each of pneumonia and bacterial bronchitis associated with valves within the first 3 months of implantation, so the rate of observed events for the primary safety objective was 2 of the 84 patients expected for follow-up at 3 months (2.4%).

Procedure-Related Complications

There were no procedure-related deaths. All events within 3 days of a bronchoscopy procedure were reviewed. There were 8 episodes of dyspnea and wheezing after bronchoscopy that were classified as bronchospasm. One was serious and associated with respiratory failure and myocardial infarction that began the evening after an uneventful procedure [15]. This patient had further episodes of bronchospasm, and therefore proceeded to uncomplicated valve removal on day 21. A second patient had all valves removed on day 3 because the bronchospasm did not resolve. Three additional episodes of bronchospasm resolved promptly after nebulizer treatments and 2 resolved with additional treatment.

Other complications associated with study procedures included: 1 patient who suffered a myocardial infarction on day 3; 3 episodes where valve placements were inadvertently deeper than the desired target locations with resultant injury to the bronchi, and 2 patients with transient hypercarbia (with 1 requiring overnight ventilatory support).

Protocol-Specified Safety Measures

Other safety measures specified by the protocol are summarized in table 6. These are events that were device-related. Another specified safety measure was a hospitalization >3 days after the initial procedure, which occurred in 9 patients. Cough was considered an AE if it persisted beyond 3 days after the procedure; this occurred in only 1 patient.

Other Severe or Serious AEs

The investigators judged that 7 patients had AEs that were serious or severe and definitely device-related. Five of these were episodes of pneumothorax and are discussed in detail below. One had episodes of bronchospasm starting after the procedure and is discussed above. One had a sequence of events that began with bronchitis on day 30, then a COPD exacerbation on day 57, followed by *Pseudomonas* respiratory tract infection on day 74, and finally UL pneumonia on day 333.

Pneumonia

There were 6 episodes of pneumonia in an area of valve treatment. None occurred within 3 months of the procedure, 2 were between 3 and 6 months and 4 were 6+ months after treatment. The overall incidence of pneumonia distal to valves within 6 months was 2.2% of subjects or 1.1% of lobes treated (6.6% of subjects or 3.4% of lobes treated within 12 months).

Pneumothorax

Three patients had pneumothorax with prolonged air leaks (3.3%) and 2 were among the 3 deaths directly or indirectly related to pneumothorax. One patient died from tension pneumothorax occurring during sleep 4 days after valve placement. The procedure in this patient was uneventful and the chest film after the procedure showed no atelectasis. A patient expired on day 113 from respiratory failure and pneumonia resulting from COPD exacerbation on day 81 and pneumothorax on day 91.

One patient died on day 33 related to respiratory failure and pneumonia after an intra-operative tension pneumothorax on day 20 during placement of a double-lumen endotracheal tube in preparation for surgical repair of a prolonged air leak after pneumothorax with lobar atelectasis which began on day 1.

During the 12-month study, there were a total of 11 patients that experienced pneumothorax (12.1%). This does not include 1 patient that had a pneumothorax following needle aspiration of a nodular density. Five patients underwent chest tube insertion for pneumothorax that occurred in the hospital and 1 patient developed a pneumothorax in hospital which resolved without tube drainage. One patient had the pneumothorax worsen after discharge and then received chest tube treatment. Four patients experienced delayed-onset pneumothorax 4 (2 patients), 9 and 91 days after the procedure.

Analysis of pneumothorax data in this pilot study showed that 5 patients with pneumothorax on the left side had treatment of the lingula in addition to the ULs. Only 17 patients had complete left UL treatment (lingula included) so this was a 29% incidence. The treatment algorithm was subsequently modified to exclude treatment of the lingular segments of the left UL. There were 2 episodes of left pneumothorax after modification of the treatment algorithm, but these were iatrogenic and not device-related.

Device Removal

Valve removal was performed (44 valves in 16 patients) for pneumonia, bronchospasm, recurrent COPD exacerbations, or pneumothorax. Valves were removed when there was concern about possible pneumonia in an area near a valve location (6 patients). These removals were 97, 105, 216, 265, 358, and 358 days after device placement. There were 3 valves removed in each of 5 patients and 1 valve was removed in 1 patient for a total of 16 valves removed. A total of 23 valves were removed from 3 patients for persistent or recurrent bronchospasm after the procedure (2 cases on days 3 and 21), and recurrent exacerbations of COPD (1 case on day 377). In 2 cases of pneumothorax with persistent atelectasis and air leak, 5 valves were removed on days 15 and 26.

Discussion

The primary outcome measure for this pilot study of bronchoscopic treatment with the IBV Valve was safety based on the incidence of valve migration, erosion, or infection. With no migration or erosion and a rate of associated infection <2.5%, we conclude that this study achieved the primary safety outcome goal.

The secondary endpoint for the study was effectiveness based on FEV_1, 6MWT, and SGRQ. The mean SGRQ change exceeded a clinically meaningful [20] 4-point change at all time points and was statistically significant compared to baseline at all time points. This improvement is notable because it was additive to ongoing treatment in patients that have few additional therapeutic options beyond risk reduction, medical therapy, and pulmonary rehabilitation.

HRQL (measured by the SGRQ) is arguably the most appropriate endpoint for palliative treatment. Unlike physiologic or functional tests, the SGRQ was designed to measure multiple mechanisms of improvement simultaneously [21]. Given that bronchial valve treatment putatively has multiple mechanisms of action, the SGRQ may be particularly advantageous for assessing bronchial valve treatment of emphysema.

There are at least three mechanisms for improvement with bronchial valve treatment. The original hypothesis was that blocking an airway would cause lobar atelectasis to emulate lung volume reduction (reported by Toma et al. [10] in 2003). The second mechanism is the reduction of dynamic hyperinflation (reported by Hopkinson et al. [22] in 2005). We are disappointed that in a multicenter trial that used clinical laboratories, we were not able to test for dynamic hyperinflation during exercise. The third mechanism is the interlobar shift of ventilation from the treated UL to the untreated lung zones identified by serial QCT as reported in 2008 [17]. The redirection of ventilation combined with the change in perfusion ratios reported here lends support to the concept that the redistribution of ventilation/perfusion results in improved ventilation/perfusion matching, and that this ultimately translated into documented improvements in HRQL. The correlation between QCT changes and HRQL improvements seen in this pilot study supports this hypothesis. Patients may improve with one or more of these mechanisms of action; thus, these mechanisms are not mutually exclusive, although the safety associated with each will be different.

Given the fact that neither FEV_1 nor 6MWT results showed significant improvement in this study, it raises the concern that the significant SGRQ improvements seen in this trial could be due to a placebo effect. We think not because the regional lung volume changes found with serial QCT are unlikely to be due to a placebo effect, and these QCT changes correlated highly with the SGRQ improvements [17].

FEV_1 is appropriate for assessment of asthma therapy and measuring the degree of airflow obstruction in COPD. The question is whether FEV_1 is a good measure of treatment effect in studies of severe emphysema where patients have *fixed* obstruction and those with reversible airflow obstruction are excluded from the study. As with total lung volume measures by body plethysmography, FEV_1 cannot assess a *regional* effect of treatment, especially with an intervention that blocks about a third of each lung from ventilation. Considering this degree of reduction in ventilation, it is remarkable that the postoperative FEV_1 remained stable, rather than decreasing, implying improvement in expiratory airflow in untreated lobes. In addition, FEV_1 is effort-dependent, has more variability in severe than mild COPD, and, with the loss of elastic recoil in severe emphysema, FEV_1 can be negatively effort-dependent [23, 24], all of which can limit its utility as an outcome measure.

Pulmonary rehabilitation for severe COPD does not change FEV_1 but significantly improves dyspnea, exercise performance, and HRQL [25]. A pharmacotherapy study has shown that improvements in exercise endurance time and exertional dyspnea did not correlate with changes in FEV_1 [26]. Dyspnea is also a better predictor for survival than FEV_1 in severe COPD [27]. Therefore, FEV_1 is not a sensitive indicator at this phase of the disease [28] and this may be the reason that changes in FEV_1 were not observed.

Exercise tests may lack sensitivity and specificity as endpoints in severe COPD. It has been shown that patients with advanced COPD show a greater loss in exercise capacity than in FEV_1 percent predicted [29]. The 6MWT is attractive because of its low complexity, but is considered more a test of endurance, and only has moderate correlation with other outcome variables in COPD such as HRQL [30]. When the 6MWT test is severely reduced it becomes a reliable predictor of mortality in COPD, but this may be due to loss of muscle mass and peripheral muscle dysfunction [31, 32] rather than solely a decrement in respiratory function. In addition, the 6MWT results can be confounded by the use of supplemental oxygen, effort, and practice, and the results can be affected by the function of non-respiratory issues [33], including psychological factors [34]. Even studies of the 6MWT for predicted values vary by up to 30% [33], and >50% of patients with surgery in the NETT had no improvement in the 6MWT [5]. Cycle ergometry is less studied in this patient population because of complexity, expense, and technologist training [33] and, like 6MWT, may be confounded in this severe patient population. Therefore, the lack of a measured bronchial valve treatment effect on these exercise tests may be due to the inherent limitations of these tests.

The procedure and device safety results deserve more comment. Not surprisingly, advanced age is associated with more procedure complications in patients with severe COPD [16]. Bronchospasm after bronchoscopy is a well-known complication [35]. Pneumothorax and prolonged air leak have been reported as complications with both LVRS and bronchoscopic treatment of emphysema [36, 10]. The development of pneumothorax after bronchoscopic valve treatment is presumably due to tension on adjacent tissue, overexpansion of blebs or bullae, or adhesions when lobar or segmental lung volume reduction occurs, and there is an association between induction of lobar atelectasis and pneumothorax [16]. Therefore, complete or total treatment of all airways within a single lobe would be expected to be associated with a greater incidence of pneumothorax as a result of decreased intralobar collateral ventilation and greater expected incidence of lobar atelectasis. We observed pneumothorax in 5 of 17 patients when treatment of the lingular segments was added to left UL treatment. Therefore, avoidance of occlusion of every airway of a single lobe may be prudent until there is a proven method to predict which patients are at greatest risk for pneumothorax.

LVRS is an option for select patients with emphysema but has significant morbidity and mortality. In the NETT, 30-day morbidity for major pulmonary and cardiac complications, e.g. mechanical ventilation for >3 days, re-intubation, pulmonary embolism, myocardial infarction, and arrhythmia requiring treatment, was 49.8% [7]. The comparable rate in this trial with bronchial valve treatment was 5.5%. Mortality, due to all causes within 90 days for the non-high-risk surgical cohort in the NETT was 5.8% [5], whereas in this trial it was 3.3%. The HRQL results measured at 6 months by SGRQ with LVRS in the NETT achieved a peak improvement of –11.3 points with 60% of patients responding (–4-point threshold) compared to an improvement of –8.2 points and a 55% responder rate with bronchial valve treatment. This suggests that bronchial valve treatment has a favorable risk/benefit ratio, at least in terms of HRQL, compared to LVRS.

There are limitations to the conclusions from this study. As a pilot trial there was no control group, thus a double-blind, randomized, controlled study is necessary to assess the extent by which the observed changes in HRQL and effort-dependent pulmonary and exercise

tests may be affected by a placebo effect or patient dropout. The regional volume changes demonstrated on QCT are less likely to be impacted by a placebo effect. A randomized, controlled trial will also be needed to assess if the incidence of COPD exacerbations is altered by bronchial valve treatment. The annual rate of exacerbations in this study calculates to 1.05/year, which falls between the treatment and control group rates (0.85 and 1.13) in the TORCH trial, although that study enrolled patients with more moderate COPD (mean FEV_1 44% of predicted) [37]. The exacerbation rate reported in the NETT control group was 0.37/year, but this only included COPD exacerbations requiring hospitalization [38]. Using a similar criterion, the rate in this study was 0.46/year; therefore the COPD exacerbation rate is probably not increased with bronchial valve treatment compared to the published literature. Another limitation of this trial is the loss of data secondary to patient withdrawals. Although our trial withdrawals were less than seen in other COPD trials [28], withdrawals are unavoidable when working with patients with severe disease and may bias long-term results.

Pilot trials have also been done with another bronchial valve and results have been published in a summary report [39]. The investigators in this composite experience described a 90-day mortality rate of 1.02%, and that 46% of patients had clinically significant improvement in FEV_1 and 55% in 6MWT 90 days after the procedure. A treatment strategy of complete lobar exclusion of a single lobe appeared to provide the greatest magnitude of benefit. Since they did not use uniform protocols, patient selection, or treatment strategies it is not possible to compare results, but the safety of the procedure was established. It may well be that the improvements in FEV_1 and 6MWT seen in this non-randomized composite study may be related to the focus on complete, unilobar treatment aiming for the mechanism of action of lung volume reduction by induction of atelectasis in patients with minimal interlobar collateral ventilation. The major concern with complete lobar occlusion is an increased incidence of pneumothorax with rapid induction of atelectasis, which may mitigate the clinical benefits seen with this treatment approach. A randomized trial with that device [40] was completed in 2006 [41], but the results have not yet been published.

In summary, bilateral bronchial valve treatment is a promising treatment for severe COPD with UL-predominant emphysema. We have elucidated a third mechanism of action from bronchial valve treatment: redirection of ventilation to the untreated, healthier lung parenchyma. This redirection of ventilation likely results in improved ventilation/perfusion matching by blocking ventilation to the most diseased lung. This mechanism, similar to reduction in dynamic hyperinflation, is not dependent on lobar atelectasis with the risk of pneumothorax. The primary outcome goal of safety was demonstrated in this trial, and the overall safety profile compares favorably to LVRS. Bronchial valve treatment of severe emphysema needs to be studied further, but may represent another treatment option for the large number of patients worldwide with this debilitating disease.

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References

1 Mannino DM, Buist AS: Global burden of COPD: risk factors, prevalence, and future trends. Lancet 2007:370:765–773.
2 Rennard S, Decramer M, Calverley PM, Pride NB, Soriano JB, Vermeire PA, Vestbol J: Impact of COPD in North America and Europe in 2000: subjects' perspective of Confronting COPD International Survey. Eur Respir J 2002;20:799–805.
3 Celli BR: Update on management of COPD. Chest 2008;133:1451–1462.
4 Make BJ, Martinez FJ: Assessment of patients with chronic obstructive pulmonary disease. Proc Am Thorac Soc 2008;5:884–890.
5 National Emphysema Treatment Trial Research Group: A randomized trial comparing lung volume reduction with medical therapy for severe emphysema. N Engl J Med 2003;348:2059–2073.
6 Naunheim KS, Wood DE, Mohsenifar Z, Sternberg AL, Criner GJ, DeCamp MM, Deschamps CC, Martinez FJ, Sciurba FC, Tonascia J, Fishman AP: Long-term follow-up of patients receiving lung-volume-reduction surgery versus medical therapy for severe emphysema by the National Emphysema Treatment Trial Research Group. Ann Thorac Surg 2006;82:431–443.
7 Naunheim KS, Wood DE, Krasna MJ, DeCamp MM Jr, Ginsburg ME, McKenna RJ, Criner GJ, Hoffman E, Sternberg AL, Deschamps C, for the National Emphysema Treatment Trial Research Group: Predictors of operative mortality and cardiopulmonary morbidity in the National Emphysema Treatment Trial. J Thorac Cardiovasc Surg 2006; 131:43–53.
8 Naunheim K: Lung-volume reduction surgery: a vanishing operation? J Thorac Cardiovasc Surg 2007;133:1412–1413.
9 Sabanathan S, Richardson J, Pieri-Davis S: Bronchoscopic lung volume reduction. J Cardiovasc Surg (Torino) 2003;44:101–108.
10 Toma TP, Hopkinson NS, Hillier J, Hansell DM, Morgan C, Goldstraw PG, et al: Bronchoscopic volume reduction with valve implants in patients with severe emphysema. Lancet 2003:361:931–933.
11 Snell GI, Holsworth L, Borrill ZL, Thomson KR, Kalff V, Smith JA, Williams TJ: The potential for bronchoscopic lung volume reduction using bronchial prostheses: a pilot study. Chest 2003;124:1073–1080.
12 Ingenito EP, Berger RL, Henderson AC, Reilly JJ, Larry Tsai L, Hoffman A: Bronchoscopic lung volume reduction using tissue engineering principles. Am J Respir Crit Care Med 2003;167:771–778.
13 Rendina EA, De Giacomo T, Venuta F, Coloni GF, Meyers BF, Patterson GA, Cooper JD: Feasibility and safety of the airway bypass procedure for patients with emphysema. J Thorac Cardiovasc Surg 2003;125:1294–1299.
14 FDA News: FDA Approves Lung Valve to Control Some Air Leaks after Surgery (cited June 26, 2009). http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116970.htm
15 Wood DE, McKenna RJ Jr, Yusen RD, Sterman DH, Ost DE, Springmeyer SC, et al: A multicenter trial of an intrabronchial valve for treatment of severe emphysema. J Thorac Cardiovasc Surg 2007;133:65–73.
16 Springmeyer SC, Bolliger CT, Waddell TK, Gonzalez X, Wood DE: Treatment of heterogeneous emphysema using the Spiration IBV valves. Thorac Surg Clin 2009;19:247–253.
17 Coxson HO, Nasute Fauerbach PV, Storness-Bliss C, Muller NL, Cogswell S, Dillard DH, et al: The computed tomography assessment of lung volume changes after bronchial valve treatment. Eur Respir J 2008;32:1443–1450.
18 Gelb AF, Gutierrez CA, Weisman IM, Newsom R, Taylor CF, Zamel N: Simplified detection of dynamic hyperinflation. Chest 2004; 126:1855–1860.
19 National Emphysema Treatment Trial Research Group: Rationale and design of the National Emphysema Treatment Trial. A prospective randomized trial of lung volume reduction surgery. Chest 1999;116:1750–1761.
20 Jones PW: Interpreting thresholds for a clinically significant change in health status in asthma and COPD. Eur Respir J 2002;19: 398–404.
21 Jones PW: Health status measurement in chronic obstructive pulmonary disease. Thorax 2001;56:880–887.
22 Hopkinson NS, Toma TP, Hansell DM, Goldstraw P, Moxham J, Geddes DM, et al: Effect of bronchoscopic lung volume reduction on dynamic hyperinflation and exercise in emphysema. Am J Respir Crit Care Med 2005;171:453–460.
23 Krowka MJ, Enright PL, Rodarte JR, Hyatt RE: Effect of effort on measurement of forced expiratory volume in one second. Am Rev Respir Dis 1987;136:829–833.
24 Suratt PM, Hooe DM, Owens DA, Anne A: Effect of maximal versus submaximal expiratory effort on spirometric values. Respiration 1981;42:233–236.
25 Nici L, ZuWallack R, Wouters E, Donner CF: On pulmonary rehabilitation and the flight of the bumblebee: the ATS/ERS Statement on Pulmonary Rehabilitation. Eur Respir J 2006;28:461–462.
26 O'Donnell DE, Lam M, Webb KA: Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;160:542–549.
27 Nishimura K, Izumi T, Tsukino M, Oga T: Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. Chest 2002;121:1434–1440.
28 Reilly J: COPD and declining FEV_1 – time to divide and conquer? N Engl J Med 2008;359: 1616–1618.
29 Casanova C, Cote CG, Marin JM, de Torres JP, Aguirre-Jaime A, Mendez R, et al: The six-minute walk test: long-term follow up in patients with COPD. Eur Respir J 2007;29: 535–540.
30 Wise RA, Brown CD: Minimally clinically important differences in the six-minute walk test and the incremental shuttle walking test. COPD 2005;2:125–129.
31 Landbo C, Prescott E, Lange P, Vestbo J, Almdal TP: Prognostic value of nutritional status in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;160: 1856–1861.
32 Schols AM, Slangen J, Volovics L, Wouters EF: Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157: 1791–1797.

33 Chetta A, Pisi G, Aiello M, Tzani P, Olivieri D: The walking capacity assessment in the respiratory patient. Respiration 2009;77:361–367.
34 Ingle L, Rigby AS, Nabb S, Jones PK, Clark AL, Cleland JG: Clinical determinants of poor six-minute walk test performance in patients with left ventricular systolic dysfunction and no major structural heart disease. Eur J Heart Fail 2006;8:321–325.
35 Colt HG, Matsuo T: Hospital charges attributable to bronchoscopy-related complications in outpatients. Respiration 2001;68:67–72.
36 Cooper JD, Trulock EP, Triantafillou AN, Patterson GA, Pohl MD, Deloney PA, Sundaresan RS, Roper CL: Bilateral pneumectomy (volume reduction) for chronic obstructive pulmonary disease. J Thorac Cardiovasc Surg 1995;109:106–116.
37 Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J: Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007;356:775–789.
38 Washko GR, Fan VS, Ramsey SD, Mohsenifar Z, Martinez F, Make BJ, Sciurba FC, Criner GJ, Minai O, Decamp MM, et al: The effect of lung volume reduction surgery on chronic obstructive pulmonary disease exacerbations. Am J Respir Crit Care Med 2008;177:164–169.
39 Wan IYP, Toma TP, Geddes DM, et al: Bronchoscopic lung volume reduction for end-stage emphysema. Chest 2006;129:518–526.
40 Strange C, Herth FJF, Kovitz KL, et al: Design of the endobronchial valve for emphysema palliation trial (VENT): a nonsurgical method of lung volume reduction. BMC Pulm Med 2007;7:10.
41 Pulmonx: Clinical information: VENT Study. http://www.pulmonx.com/clinical-information/vent-study/index.html.