OLYMPUS®

Your Vision, Our Future

BRONCHIAL VALVE TREATMENT: PAST, PRESENT AND FUTURE

With Learnings from the US IBV™* Valve Bilateral-Partial Treatment Trial

Proceedings of Olympus Meeting
American Thoracic Society International Conference,
May 20, 2012

These proceedings are intended for audiences in Europe, Australia, New Zealand and other countries where the IBV Valve System has been approved for the treatment of diseased lung in emphysematous patients. In the USA, the IBV Valve System is not approved for emphysema, and has a Humanitarian Device Exemption for the treatment of specific post-surgical air leaks.

INTRODUCTION

Treatment with bronchial valves in patients with severe emphysema was developed to achieve lobar volume reduction without the risks of mortality and morbidity associated with surgical procedures. The technical approach to using bronchial valves has evolved over time, using the learnings from a range of clinical studies.

This educational program, held at the American Thoracic Society (ATS) International Conference in San Francisco 2012, brought together a group of experts in the field of bronchial valve therapy to present an overview of the clinical experience in this field. The presentations covered the background to the development of valves; a summary of the clinical data to date, specifically with respect to the IBV Valve System; and the direction for future valve therapy.

The meeting was sponsored by Olympus, and was intended for international attendees from countries where the IBV Valve System is approved to treat diseased lung in emphysematous patients, or damaged lung resulting in air leaks, by limiting airflow to selected areas. In the USA, the IBV Valve System is not approved for emphysema, and has a Humanitarian Device Exemption for the treatment of specific post-surgical air leaks.

The session was chaired by:

Robert Wise, MD
John Hopkins University, Baltimore, USA

Arschang Valipour, MD
Otto Wagner Hospital, Vienna, Austria

Daniel Sterman, MD
University of Pennsylvania, Philadelphia, USA

The distinguished faculty presenting at the session were:

Christopher Cooper
MD, FRCP, FACSM, FCCP
University of California, Los Angeles, USA

Daniel Nader
DO, FCCP, FACP
Oklahoma State University Center for Health Sciences and Southwestern Regional Medical Center, Tulsa, USA

Mark Elstad, MD
University of Utah, Salt Lake City, USA

Harvey Coxson, PhD
University of British Columbia, Vancouver, Canada

Felix Herth
MD, PhD, FCCP
University of Heidelberg, Heidelberg, Germany

The following summary provides an overview and key conclusions of the meeting >>

BACKGROUND AND RATIONALE FOR BRONCHIAL VALVES

In 2004, the World Health Organization (WHO) estimated the number of people to have chronic obstructive pulmonary disease (COPD) to be 64 million and deaths from COPD are projected to increase by more than 30% in the next 10 years [WHO, 2011]. Worldwide prevalence of COPD ranges from 7.6% to 10.1% [Halbert, 2006; Buist, 2007]. Emphysema, characterized by parenchymal destruction, affects an estimated 1.8% of the population worldwide [Halbert, 2006].

The airflow limitation associated with COPD, and the resulting air trapping and hyperinflation in the lungs, is the result of both an increase in airway resistance and the reduced driving pressure for lung deflation that comes from static elastic lung recoil. Hyperinflation has been shown to be directly associated with patient-centered outcomes such as dyspnea and exercise limitation, both of which have an impact on health-related quality of life (QOL) [Cooper, 2006].

Pharmacological treatment for severe emphysema usually involves a combination of different classes of bronchodilators and often a third treatment such as an inhaled corticosteroid, roflumilast or azithromycin [Cooper, 2005]. For patients with advanced emphysema who have maximized their medical treatment, other options include non-pharmacological interventions such as volume reduction strategies and lung transplantation.

Unmet needs in advanced emphysema treatment

The current unmet needs in relation to the treatment of advanced emphysema are:

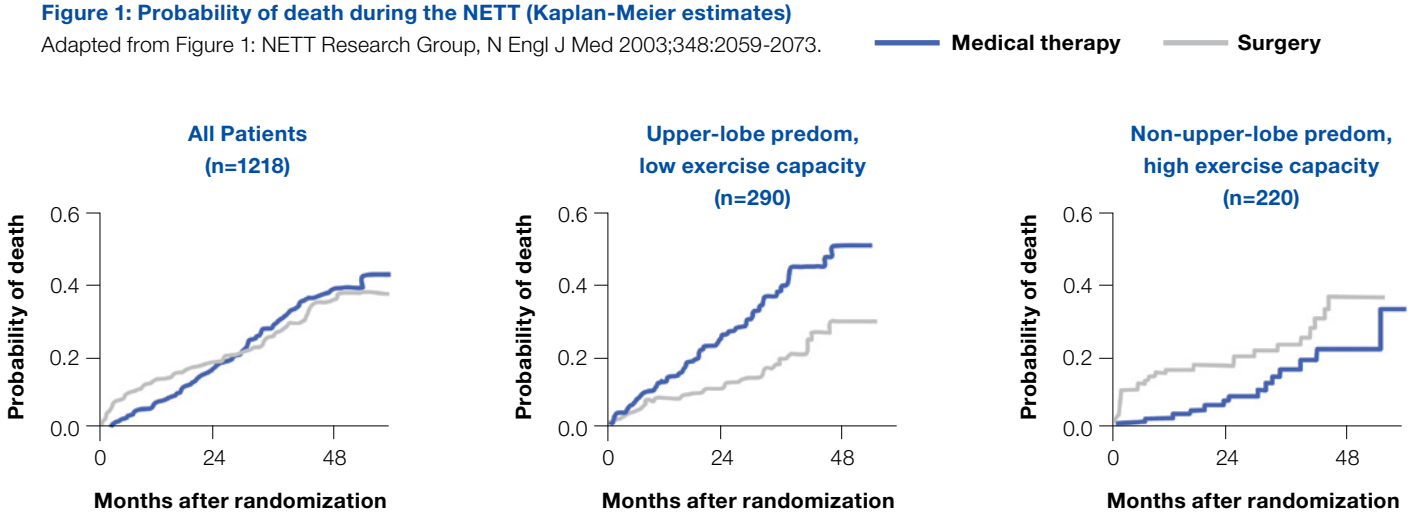
- **Need for less invasive options for the most severe patients**
  - Surgical options have substantial risks with long recovery periods
  - Surgical options are available to only a few selected patients
- **Need for additional options beyond medical therapy for emphysema**
  - Medications alone may not modify the long-term decline in lung function and QOL
- **Need for improved quality of life**
  - COPD patients often have poor QOL and functional status despite pharmacological and rehabilitative therapies

Goals of bronchial valve therapy

During the 1990s there was a renewed interest in the treatment of severe emphysema with surgical procedures such as lung volume reduction surgery (LVRS) [Cooper, 1995; McKenna, 1996]. Subsequently, the National Emphysema Treatment Trial (NETT) compared the effects of LVRS with medical therapy and showed significant survival benefit in the LVRS group for a subgroup of patients with upper lobe-predominant disease and low exercise capacity [NETT Research Group, 2003] (Figure 1).

Figure 1: Probability of death during the NETT (Kaplan-Meier estimates)

Adapted from Figure 1: NETT Research Group, N Engl J Med 2003;348:2059-2073.



Bronchoscopic methods to treat emphysema with one-way bronchial valves have been developed to achieve similar benefits as LVRS without the risks in morbidity and mortality associated with surgical procedures [Toma, 2003; Venuta, 2005]. The original hypothesis for the use of bronchial valves was that the placement of valves in the airways that supplied the most hyperinflated parts of the emphysematous lungs would result in lobar atelectasis and a reduction in lung volume, thus mimicking LVRS and its aims to improve pulmonary function and mortality.

The IBV Valve is an umbrella-shaped, one-way valve that is placed via a delivery catheter, introduced through the working channel of a flexible bronchoscope (Figure 2).

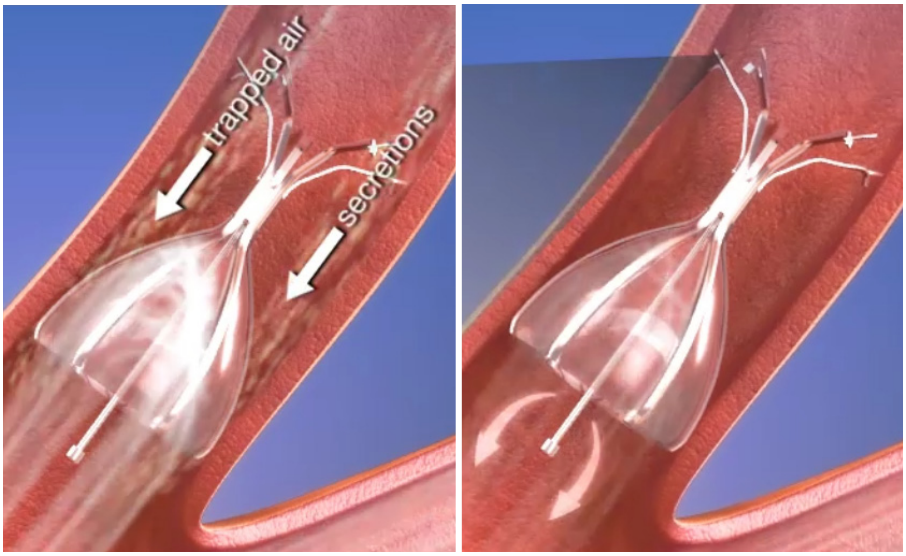
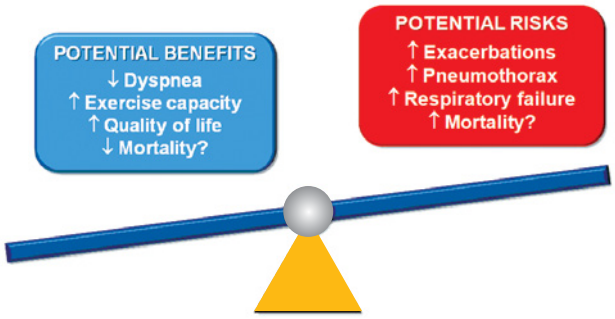


Figure 2: Diagram of the IBV Valve
The valve consists of a Nitinol frame covered with a polymer membrane and five anchors that securely engage the airway walls at the targeted treatment location. The valve limits airflow into targeted airways distal to the valve but allows mucus and air movement in the proximal direction and, if needed, is removable.

OVERVIEW OF CLINICAL STUDIES

The relative benefits and risks of bronchial valve therapy need to be assessed to identify a suitable approach that has the most favorable risk-benefit ratio across clinical and economic outcomes (Figure 3).

Figure 3: Optimizing the benefits and risks with bronchial valve therapy



The IBV Valve has been investigated in several studies, each with its own patient selection, treatment approach and study protocol (Table 1). Knowledge of the effectiveness and safety of bronchial valve therapy has evolved with each study.

Table 1: Summary of studies investigating IBV Valve therapy

Clinical Study	Treatment Approach	Screening for High Heterogeneity or Complete Fissures
Pilot Studies (2004–2006)	Bilateral occlusion without lingula (n=77), Bilateral occlusion with lingula (n=18), Single-lobe, complete occlusion (n=3)	No
European Study (2007–2009)	Bilateral, partial occlusion (n=37) v. Sham bronchoscopy (n=36)	No
US Trial (2007–2010)	Bilateral, partial occlusion (n=142) v. Sham bronchoscopy (n=135)	No
Unilateral v. Bilateral Study (2009–2011)	Single-lobe, complete occlusion (n=11) v. Bilateral, partial occlusion (n=11)	Yes

Pilot studies

Early pilot studies (n=98) evaluating IBV Valves were based on the hypothesis of achieving lobar atelectasis and a reduction in lung volume [Wood, 2007; Springmeyer, 2009; Sterman, 2010]. Patients with severe airflow obstruction, hyperinflation and with severe, upper lobe-predominant emphysema were included; and valves were placed bilaterally, consistent with the approach used with LVRS [Cooper, 1995]. Patients were not evaluated for high heterogeneity or complete fissures for collateral ventilation.

Results in all studies showed that the success rate in placing the IBV Valves was high and there was no migration or expectoration. Overall, there were no significant improvements seen in forced expiratory volume in one second (FEV_1) or 6-minute walking distance (6MWD) but over half the patients showed a clinically meaningful improvement in their health-related QOL as measured by St George's Respiratory Questionnaire (SGRQ) scores (Table 2) [Springmeyer, 2009; Sterman, 2010]. In addition, significant changes in lobar volumes (approximately 300 mL or 10% change) were demonstrated in both the treated (volume decrease) and untreated (volume increase) lobes, but the total lung volume remained unchanged [Coxson, 2008; Sterman, 2010].

Despite the lack of screening for collateral ventilation and a partial-occlusion approach in the majority of patients, atelectasis was reported in approximately 10% of patients, and in just over half of these patients there was an accompanying pneumothorax [Springmeyer, 2009]. The overall incidence of pneumothorax was reduced in those patients where the lingula was not treated. Improvements in FEV_1 were observed in the small group of patients who had atelectasis but, interestingly, the improvements in SGRQ scores were observed with and without the presence of lobar atelectasis (Table 2).

Table 2: Pulmonary function and SGRQ changes for subjects at 6 months, with and without atelectasis (ATX)

	ATX - Yes (n)	ATX - No (n)	Total (n)
TLC change (L)	-0.4 ± 0.7 (6)	-0.1 ± 0.6 (66)	-0.07 ± 0.6 (72)
RV change (L)	-0.7 ± 1.0 (6)	0.1 ± 0.8 (66)	0.0 ± 0.8 (72)
FEV_1 change (L)	0.14 ± 0.06 (6)	-0.04 ± 0.16 (68)	-0.02 ± 0.16 (74)
SGRQ change	-15.3 ± 14 (6)	-7.3 ±16 (64)	-8.0 ±16 (70)
SGRQ responders	5/6 (83%)	34/64 (53.1%)	39/70 (55.7%)

TLC: total lung capacity; RV: residual volume; FEV1: forced expiratory volume in 1 second; SGRQ: St George's Respiratory Questionnaire.
Adapted from: Springmeyer, Thorac Surg Clin 2009;19:247-253.

The conclusions from the pilot studies with the IBV Valve System suggested that a bilateral, partial-occlusion treatment with IBV Valves could mitigate the risk of pneumothorax while enabling a significant redirection of lung volumes from the treated upper lobes to the non-treated lobes, and moderate improvements in health status for a proportion of patients. The subsequent studies were therefore designed using a bilateral, partial-occlusion treatment approach.

European Study for the Treatment of Advanced Emphysema with Bronchial Valves

This study was the first multicenter, blinded, sham-controlled study to assess the safety and effectiveness of IBV Valve therapy in patients with upper lobe-predominant severe emphysema, using a bilateral, partialocclusion treatment approach without the goal of lobar atelectasis [Ninane, 2012]. Patients were not evaluated for high heterogeneity or complete fissures for collateral ventilation. A composite primary endpoint was used; a positive responder was defined as having both a ≥ 4 point improvement in SGRQ and a lobar volume shift as measured by quantitative computed tomography (QCT) at 3 months.

Seventy-three patients were randomized to bronchoscopy with (n=37) or without (n=36) bronchial valves. The procedure and devices were well tolerated; there was no valve migration or erosion, and no expectoration of valves. The incidence of adverse events was similar in the treated and control groups and there was no atelectasis and/or pneumothorax.

At the end of three months' blinded treatment, a positive treatment response was seen in 8 of 33 patients (24%) in the treatment group, compared with 0 of 35 patients in the control group (p=0.002) (Table 3). Treatment with the valves resulted in a significant decrease in upper lobe lung volumes, and a significant corresponding increase in non-treated lobe volumes compared with minimal changes in the control group. There were no significant changes in other efficacy endpoints following treatment including mean values for FEV_1, 6MWD or modified Medical Research Council (mMRC) dyspnea scale scores.

Table 3: Percent responders and change from baseline in CT lung volumes and SGRQ score at 3 months (European Study)

	Treatment (n=33)	Control (n=35)	p-value
CT volumes + SGRQ responders (patients)	8 of 33	0 of 35	0.002
CT lung volumes (% change) *Upper lobes (treated)* *Non-upper lobes (untreated)*	 -7.3 ± 9 6.7 ± 14.5	 0.7 ± 5.2 0.2 ± 7.8	 <0.0001 0.027
SGRQ total score	-4.3 ± 16.2	-3.6 ± 10.7	0.837

CT: Computed tomography; SGRQ: St George's Respiratory Questionnaire.

Adapted from: Ninane, Eur Respir J 2012;39:1319-1325.

US IBV Valve Bilateral-Partial Treatment Trial

In parallel, a multicenter, randomized, blinded, controlled trial was conducted in the US, which also evaluated the safety and effectiveness of a bilateral, partial-occlusion treatment approach in patients with severe, upper lobe-predominant emphysema [Nader, 2012; Elstad, 2012; Coxson, 2012; Wood, 2012]. As with previous studies, patients were not evaluated for high heterogeneity or complete fissures for collateral ventilation. A positive responder was defined as having both a >4 point improvement in SGRQ and a lobar volume shift (10% increase in non-upper lobe and any decrease in upper lobe) as measured by QCT at 6 months.

A total of 277 patients were randomized, 142 to treatment with valves and 135 to sham bronchoscopy; 121 and 134 patients respectively, completed the 6 month follow-up visit. The technical performance of the IBV Valve System was successful and consistent with earlier studies: 99% of valves were successfully placed at target locations; and no valve migration, erosion or expectoration occurred.

The incidence of serious adverse events was significantly higher in the treated (20 patients [14%]) versus control (5 patients [4%]) groups [Elstad, 2012]. During the 6 month study, there were six deaths in the treated group versus one in the control group, of which 1, in the treated group, was assessed as probably related to the procedure and none were assessed as device-related. Serious pneumothorax occurred in 3 treated patients versus none in the control group but this incidence was mitigated when the treatment algorithm was changed after enrollment of the 37th patient from using a total right and partial left occlusion algorithm to partial right and partial left occlusion algorithm. Conscious sedation used by some sites was associated with a higher incidence of serious procedural adverse events (19%) compared with the overall study incidence (6%). The use of anesthesia with intubation and mechanical ventilation resulted in a shorter procedure duration and was found to be safer than conscious sedation.

After 6 months' blinded treatment, the responder rate was significantly higher after treatment (6/121 [5.0%]) versus control (1/134 [0.7%]), but this improvement was not considered clinically meaningful (Table 4). In patients who received valves, there was a significant shift in lobar volume from the treated upper lobes to the untreated lobes but this was smaller than expected and was not associated with any significant changes in SGRQ scores. There were no significant improvements in other endpoints (lung function and exercise capacity) in the treated versus control groups.

Table 4: Percent responders and change from baseline in CT lung volumes and SGRQ score at 6 months (US Trial)

	Treatment (n=142)	Control (n=135)	95% BCI of treatment difference
CT volumes + SGRQ responders, n(%)	6 of 121 (5.0)	1 of 134 (0.7)	(0.048%, 9.212%)
CT lung volumes, n *Upper lobes, mL* *Upper lobes, %* *Non-upper lobes, mL* *Non-upper lobes, %*	120 -224 ± 299 -6.4 ± 8.0 214 ± 384 7.0 ± 13.8	133 -17 ± 204 -0.4 ± 5.3 -27 ± 292 -0.9 ± 9.1	 (-272, -143) (155, 326)
SGRQ total score	+2.15 ± 16.36	-1.41 ± 11.26	(0.4, 7.0)

CT: Computed tomography; SGRQ: St George's Respiratory Questionnaire.

Data on file

The results of the US IBV Valve Trial confirmed that the bilateral, partial-occlusion approach with bronchial valve therapy mitigated the incidence of atelectasis and/or pneumothorax, but may also have contributed to the reduced target lobe volume changes and the lack of clinically meaningful responder rates.

Predictors of response to bronchial valve therapy, and implications for patient selection

The lessons from the IBV Valve studies have been augmented by the VENT study, a multicenter trial evaluating Endobronchial Valve (EBV) treatment in 321 patients with advanced heterogeneous emphysema, using a single-lobe, complete-occlusion approach. That trial showed modest improvements in the primary endpoint (percent change in FEV_1) for the whole group but an enhanced treatment response in a subgroup of patients with greater radiographic evidence of emphysema heterogeneity and fissure completeness (Table 5) [Sciurba, 2010]. There was an increased rate of COPD exacerbations in the first 90 days in the EBV-treated group compared with the control group, receiving standard medical care (7.9% v. 1.1%, p=0.03). At 6 months, there were six deaths (2.8%) in the EBV-treated group compared with none in the control group; at 12 months the rate of deaths was similar in the two groups (3.7% v. 3.5% respectively). These findings revealed that careful screening of patients with high heterogeneity and complete fissures may be an important predictor of good outcomes with bronchial valve treatment.

Table 5: Percent changes in the FEV1 and distance on the 6-Minute Walk Test at 6 and 12 months, according to subgroup of disease severity (VENT study)

	Percent change from baseline at 6 mo		Percent change from baseline at 12 mo	
Subgroup and Outcome	**Difference between EBV and control group % (95% CI)**	**p-value†**	**Difference between EBV and control group % (95% CI)**	**p-value†**
High heterogeneity				
FEV_1	10.7 (3.5 to 17.9)	0.004	13.3 (5.7 to 20.9)	<0.001
Distance walked on 6-min walk test	12.4 (4.8 to 20.1)	0.002	7.1 (-0.8 to 14.9)	0.08
Low heterogeneity				
FEV_1	2.5 (-3.1 to 8.2)	0.38	1.5 (-4.7 to 7.6)	0.64
Distance walked on 6-min walk test	-1.0 (-6.4 to 8.4)	0.80	-0.6 (-6.4 to 7.7)	0.84
Complete fissure				
FEV_1	16.2 (8.8 to 23.8)	<0.001	17.9 (9.8 to 25.9)	<0.001
Distance walked on 6-min walk test	7.7 (-1.8 to 17.2)	0.14	3.9 (-4.0 to 11.8)	0.31
Incomplete fissure				
FEV_1	2.0 (-3.9 to 7.9)	0.51	2.8 (-3.8 to 9.4)	0.41
Distance walked on 6-min walk test	5.3 (-1.5 to 12.2)	0.13	4.5 (-2.7 to 11.8)	0.20

†All p-values are two-sided.

Adapted from: Sciurba, N Engl J Med 2010;363:1233-1244.

Complete Unilateral Versus Partial Bilateral Endoscopic Lung Volume Reduction Study

In light of these findings, an illuminating study was conducted comparing single-lobe, complete-occlusion versus bilateral, partial-occlusion approaches with the IBV Valve to determine which technique achieved the greatest improvements in efficacy among patients with bilateral heterogeneous emphysema [Eberhardt, 2012]. In addition, patients were screened using CT and perfusion scan analysis for high heterogeneity. Twenty-two patients were randomly assigned to IBV Valve treatment with either unilateral, complete occlusion of the single worst lobe (11 patients) or bilateral treatment of either the lower or upper lobes leaving one segment not treated on each side (11 patients). The primary endpoint was based on improvements in FEV_1 and 6MWD after treatment.

The IBV Valves were placed successfully in both groups, and there was no migration of valves. Four exacerbations, two per group, requiring antibiotic treatment and/or steroids but not hospitalization, were reported; one patient in the unilateral group experienced a pneumothorax and two patients in the bilateral group were treated for respiratory failure. No other complications were observed and no deaths were reported.

Significant improvements in lung function and 6MWD were observed after 30 and 90 days in the unilateral group but not the bilateral group; these changes were accompanied by improvements in SGRQ scores and mMRC dyspnea scores (Table 6).

The lessons from this trial suggest that an optimal treatment approach may involve complete occlusion of the single most diseased lobe, and careful selection of appropriate patients using CT and perfusion scan analysis.

Table 6: Mean changes of the different parameters after 30 and 90 days in the unilateral and bilateral treatment groups

	Unilateral Group				Bilateral Group			
	30 day	**p-value**	**90 days**	**p-value**	**30 days**	**p-value**	**90 days**	**p-value**
Δ FEV1 (mL)	+267±154	0.001	+180±90	0.002	+13±140	0.717	-24±117	0.624
Δ IVC (mL)	+425±451	0.019	+453±300	0.019	+2±388	1.000	+15±349	0.918
Δ RV (mL)	-546±1307	0.537	-872±796	0.005	-61±990	0.765	+85±446	0.700
Δ TLC (mL)	-86±1222	0.175	-357±874	0.175	-117±1038	0.831	+122±563	0.747
Δ RV/TLC (%)	-6.3±7.1	0.032	-7.4±3.2	0.002	+0.7±5.8	0.765	+0.1±3.6	0.831
Δ 6MWD (m)	+47.8±55.7	0.014	+48.9±53.0	0.024	-25.0±81.5	0.557	-52.3±81.2	0.080
Δ SGRQ total score	-12.2±13.4	0.003	-11.8±10.6	0.007	-0.3±9.8	0.831	+2.12±8.5	0.577
mMRC (points)	-1.1±1.1	0.070	-1.2±1.25	0.023	0.0±1.0	1.000	0.0±1.3	1.000
BODE index (points)	-2.0±1.3	0.004	-1.8±1.47	0.022	+0.5±1.1	0.219	+0.6±1.6	0.289

Δ: change from baseline; data presented as mean±SD; values in bold indicate statistical significance; FEV_1: forced expiratory volume in 1 second; IVC: inspiratory vital capacity; RV: residual volume; TLC: total lung capacity; 6MWD: 6-minute walking distance; SGRQ: St George's Respiratory Questionnaire; mMRC: modified Medical Research Council dyspnea scale; BODE: body-mass index, degree of airflow obstruction, dyspnea, and exercise capacity.

Adapted from: Eberhardt, Chest 2012 (online ahead of print).

Evaluation of long-term survival in patients following bronchial valve treatment

One of the prime concerns relating to treatment by the single-lobe, complete-occlusion approach is the treatment-induced atelectasis and associated risks such as pneumothorax. However, recent long-term data on patients who received bronchial valves showed that patients with atelectasis following bronchoscopic lung volume reduction (BLVR) had a survival benefit compared with patients who did not have atelectasis (Figure 4) [Hopkinson, 2011]. CT-visible interlobar fissures have also been shown to be a favorable prognostic factor of long-term survival (Figure 5) [Venuta, 2012]. Nonetheless, the samples were small and further investigation is needed on the mortality benefit of bronchial valve treatment.

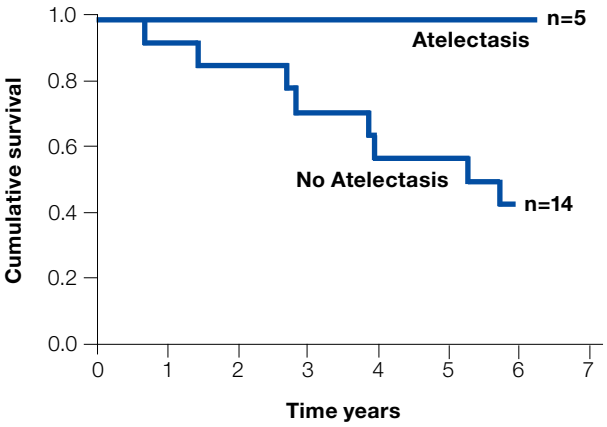


Figure 4: Atelectasis following BLVR was associated with improved survival (p=0.026)

Atelectasis: n=5; No atelectasis: n=14. Reproduced with permission of the European Respiratory Society. Eur Respir J June 2011 37:1346-1351; published ahead of print October 14, 2010, doi:10.1183/09031936.00100110

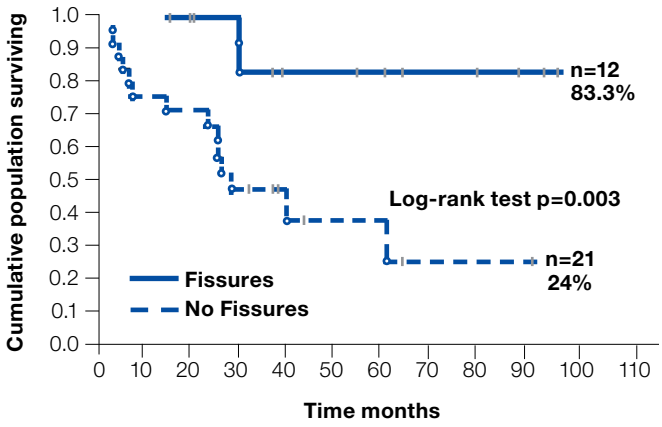


Figure 5: Survival comparison between patients with and without visible fissures

At pre-treatment: Fissures: n=15; No fissures: n=12. Reproduced with permission of the European Respiratory Society. Eur Respir J May 2012 39:1084-1089; published ahead of print October 17, 2011, doi:10.1183/09031936.00071311.

Management of pneumothorax

Given that treatment using the complete occlusion of a single lobe would be expected to be associated with an increased incidence of pneumothoraces, a clear procedure for the management of pneumothorax is recommended. This may be especially the case in patients with a rapid atelectasis, which in itself may be a predictor of good outcomes and thus should not preclude patients from consideration [Hopkinson, 2011].

Obtaining a chest radiograph 2 hours after the valve placement procedure and the following day is recommended. An asymptomatic, small pneumothorax should be monitored with no immediate action required. For patients with larger pneumothorax and associated symptoms, they should receive drainage with or without suction. If the air leak persists up to 1 week after lung expansion, it is recommended to remove one valve, leaving the target lobe partially occluded to facilitate resolution of the pneumothorax. If the air leak then resolves within a week, the valve should be replaced after 6 weeks to reinstate full occlusion of the target lobe; however, if it persists beyond another week of the valve being removed, all valves should be removed. In the rare instance that this does not resolve the air leak, video-assisted thoracoscopic surgery [VATS] with pleurodesis and/or stapling surgery is recommended.

Conclusions

The key learnings from these clinical data indicate that maximum benefits from bronchial valve therapy are achieved with greater target lobe volume reduction, as evidenced by improvements in clinical outcomes including FEV_1, 6MWD and RV. Significant lobar volume reduction is achieved following the complete occlusion of a single lobe due to the accompanying lobar volume decrease.

The development of lobar volume reduction has been shown to be most successful in patients with complete fissures due to the achievement of a ‘closed system’ [Sciurba, 2010, Gompelmann, 2010]. In addition, patients with high heterogeneity have also been shown to benefit more significantly from valve therapy [Eberhardt, 2012, Sciurba, 2010].

This approach has been shown to be significantly superior to bilateral, partial-occlusion treatment, and is associated with clinically relevant improvements in lung function, exercise capacity and quality of life. When targeting the left upper lobe, the lingula should be included. When targeting the right upper lobe, consider occluding the right middle lobe if there is an incomplete fissure between the upper lobe and the middle lobe.

Pneumothorax is a known complication of single-lobe, complete occlusion, but may be a predictor of success and can be managed by use of clear management guidelines. A higher rate of pneumothorax should be evaluated in relation to the potential to significantly improve a patient’s exercise capacity and quality of life.

Future treatments with bronchial valve therapy should use a single-lobe, complete occlusion approach in appropriately selected patients using an assessment of complete fissures and emphysema heterogeneity to increase the chances of achieving maximum lobar volume reduction, pronounced improvement in patient outcomes, and a favorable risk-benefit ratio.

REFERENCES

Buist AS, McBurnie MA, Vollmer WM *et al*: International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet 2007;370:741-750.*

Cooper CB. The connection between chronic obstructive pulmonary disease symptoms and hyperinflation and its impact on exercise and function. *Am J Med* 2006;119(10A):S21-S31.

Cooper CB, Tashkin DP. Recent developments in inhaled therapy in stable chronic obstructive pulmonary disease. *BMJ* 2005;330:640-644.

Cooper JD, Trulock EP, Triantafillou AN, Patterson GA, Pohl MS, Deloney PA, Sundaresan RS, Roper CL. Bilateral pneumectomy (volume reduction) for chronic obstructive pulmonary disease. *J Thorac Cardiovasc Surg* 1995;109:106-119.

Coxson H, Nasute Fauerbach P, Storness-Bliss C *et al*. Computed tomography assessment of lung volume changes after bronchial valve treatment. *Eur Respir J* 2008;32:1443-1450.

Coxson HO, Springmeyer S, Nader DA, Elstad MR, Chan A, Gonzalez X, Mehta AC. IBV Valve trial investigators. Bronchial valve treatment of emphysema: Lung volume reduction in a double-blind randomized trial. *Am J Respir Crit Care Med* 2012;185:A2903.

Eberhardt R, Gompelmann D, Schuhmann M, Reinhardt H, Ernst A, Heussel CP, Herth FJF. Complete unilateral versus partial bilateral endoscopic lung volume reduction in patients with bilateral lung emphysema. *Chest* 2012 (online ahead of print).

Elstad MR, Mehta AC, Nader D, Rai N, Mularski RA, Sterman DH, Gonzalez X, Springmeyer S. Bronchial valve treatment of emphysema: Procedure and device safety results from a double-blind randomized trial. *Am J Respir Crit Care Med* 2012;185:A1112.

Gompelmann D, Eberhardt R, Michaud G, Ernst A, Herth FJ. Predicting atelectasis by assessment of collateral ventilation prior to endobronchial lung volume reduction: a feasibility study. *Respiration* 2010;80(5):419-25.

Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. *Eur Respir J* 2006;28:523-532.

Hopkinson NS, Kemp SV, Toma TP, Hansell DM, Geddes DM, Shah PL, Polkey MI. Atelectasis and survival after bronchoscopic lung volume reduction for COPD. *Eur Respir J* 2011;37:1346-1351.

McKenna RJ, Brenner M, Gelb AF, Mullin M, Singh N, Peters H, Panzera J, Calmese J, Schein MJ. A randomized prospective trial of stapled lung reduction versus laser bullectomy for diffuse emphysema. *J Thorac Cardiovasc Surg* 1996;111:317-322.

Nader DA, Elstad MR, Chan A, Rai N, Mularski RA, Wise RA, Jones PW, Springmeyer SC, Gonzalez X. Bronchial valve treatment of emphysema: Study design and methods for a double-blind randomized trial. *Am J Respir Crit Care Med* 2012;185:A5924.

National Emphysema Treatment Trial Research Group: A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003;348:2059-2073.

Ninane V, Geltner C, Bezzi M, Foccoli P, Gottlieb J, Welte T, Seijo L, Zulueta JJ, Munavvar M, Rosell A, Lopez M, Jones PW, Coxson HO, Springmeyer SC, Gonzalez X. Multicentre European study for the treatment of advanced emphysema with bronchial valves. *Eur Respir J* 2012;39:1319-1325.

Sciurba FC, Ernst A, Herth FJF, Strange C, Criner GJ, Marquette CH, Kovitz KL, Chiacchierini RP, Goldin J, McLennan G, for the VENT Study Research Group. A randomized study of endobronchial valves for advanced emphysema. *N Engl J Med* 2010;363:1233-1244.

Springmeyer SC, Bollinger CT, Waddell TK, Gonzalez X, Wood DE. Treatment of heterogeneous emphysema using the Spiration IBV Valves. *Thorac Surg Clin* 2009;19:247-253.

Sterman DH, Mehta AC, Wood DE, Mathur PN, McKenna RJ, Ost DE, Truwit JD, Diaz P, Wahidi MM, Cerfolio R, Maxfield R, Musani AI, Gildea T, Sheski F, Machuzak M, Haas AR, Gonzalez HX, Springmeyer SC. A multicenter pilot study of a bronchial valve for the treatment of severe emphysema. *Respiration* 2010;79:222-233.

Toma TP, Hopkinson NS, Hillier J, Hansell DM, Morgan C, Goldstraw PG, Polkey MI, Geddes DM. Bronchoscopic volume reduction with valve implants in patients with severe emphysema. *Lancet* 2003;361:931-933.

Venuta F, di Giacomo T, Rendina EA, Ciccone AM, Diso D, Perrone A, Parola D, Anile M, Coloni GF. Bronchoscopic lung-volume reduction with one-way valves in patients with heterogeneous emphysema. *Ann Thoracic Surg* 2005;79:411-417.

Venuta F, Anile M, Diso D, Carillo C, De Giacomo T, D'Andrilli A, Fraioli F, Rendina EA, Coloni GF. Longterm follow-up after bronchoscopic lung volume reduction in patients with emphysema. *Eur Respir J* 2012;39:1084-1089.

World Health Organization fact sheet November 2011; http://www.who.int/mediacentre/factsheets/fs315/en/index.html
Last accessed 15 June 2012.

Wood DE, McKenna RJ, Yusen RD, Sterman DH, Ost DE, Springmeyer SC, Gonzalez X, Mulligan MS, Gildea T, Houck WV, Machuzak M, Mehta AC. A multicenter trial of an intrabronchial valve for treatment of severe emphysema. *J Thorac Cardiovasc Surg* 2007;133:65-73.

Wood D, Nader D, Elstad MR, Mehta AC, Sterman DH, Wise RA, Jones PW, Gonzalez X, Springmeyer SC. Bronchial valve treatment of emphysema: Results and conclusions from a double-blind randomized trial. *Am J Respir Crit Care Med* 2012;185:A5348.

CE 0050

ARTG Identifiers: 188455, 182553, 181950
WAND Reference Nos: 110725-WAND-6BJ53E, 110505-WAND-6B1TDA, 110509-WAND-6B2O34

OLIT-03633 Rev AB Article Code E0429259

OLYMPUS®

Manufactured by
SPIRATION, INC.
6675 185th Ave NE, Redmond, Washington 98052 USA

Distributed by
OLYMPUS EUROPA HOLDING GMBH
Wendenstrasse 14-18, 20097 Hamburg, Germany

KEYMED LTD.
KeyMed House, Stock Road, Southend-on-Sea, Essex, SS2 5QH, UK

OLYMPUS AUSTRALIA PTY. LTD.
31 Gilby Road, Mount Waverly, VIC., 3149, Australia