Bronchoscopic Lung Volume Reduction For Pulmonary Emphysema: Preliminary Experience With Endobronchial Occluder

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OBJECTIVE: To describe the self-expanding endobronchial occluder, as utilized in bronchoscopic lung volume reduction, with a 36 month follow-up procedure. METHODS: Twenty-three subjects with severe emphysema were recruited and underwent flexible bronchoscopic placement of self-expanding endobronchial occluders. Outcomes were assessed at 1 week, 1-month, 3-, 6-, 12-, 24-, and 36-month intervals. Feasibility, safety, and efficacy were analyzed by means of pulmonary function testing, 6-min walk test, dyspnea score, BODE (body mass index, air-flow obstruction, dyspnea, and exercise capacity) index, and St George's Respiratory Questionnaire. RESULTS: Fifty-eight self-expanding endobronchial occluders were implanted into 23 lobes previously selected. No displacement was found during the follow-up. Five subjects experienced postoperative complications of cough, and 6 subjects had lobar pneumonia, which were not located in any of the blocked segments. The FEV$_1$ in 18 subjects was improved by > 15%, compared with baselines (P < .001), and the mean first efficacy time and maximal efficacy time were 5.65 ± 1.51 months and 6.35 ± 3.08 months, respectively. No significant changes were observed in FVC or the ratio of residual volume to TLC. The 6-min walk distance, dyspnea score, and St George's Respiratory Questionnaire total score were improved in 22 subjects over a 24-month period, and a minority of subjects continued to improve through to the end of the study. Mean baseline BODE index had improved during follow-up, but not at the study's conclusion. CONCLUSIONS: This preliminary study demonstrates early significant improvements in pulmonary function, 6-min walk distance, dyspnea score, BODE index, and quality of life after placement of the self-expanding endobronchial occluder in bronchoscopic lung volume reduction. Its placement also proved both easy and safe. However, the initial improvements were maintained long-term for only a minority of subjects. *Key words: emphysema; bronchoscopic lung volume reduction; endobronchial occluder; pulmonary function; safety.* [Respir Care 2013;58(8):1351–1359. © 2013 Daedalus Enterprises]

Introduction

COPD is a major cause of chronic morbidity and mortality throughout the world, characterized by air-flow limitation that is not fully reversible.[1] In China the overall prevalence of COPD is 8.2% (men 12.4%, women 5.1%) with stage 3 (1.7%) and stage 4 (0.4%) in individuals ≥ 40 years old, and there are about 1 million deaths and over 5 million disabilities each year caused mainly by COPD.[2] So how to improve the symptoms and life quality of patients with severe COPD is an urgent social problem.

None of the existing medications for COPD has been shown to modify the long-term decline in lung function that is the hallmark of this disease.[3,4] Bronchoscopic lung volume reduction (BLVR), as an alternative to lung vol-

ume reduction surgery (LVRS), has shown promise and has reached later-stage clinical trials.[5,6] Most BLVR methods attempt to induce atelectasis by the implantation of endobronchial devices, including bronchial occluders, bronchial valves, glues, and bio-modulators. In all clinic trials to date, most patients have had selectively placed different types of one-way (expiratory) valves in the target airways.[7-9] These valves were designed to block air from entering the target area during inspiration, while allowing gas to exit during exhalation. This was intended to cause collapse and volume reduction by promoting progressive deflation in damaged regions of the lung, and reducing the potential for post-obstructive pneumonia.

However, no particular valve has proven to be consistently effective in generating atelectasis and volume reduction or producing durable clinical benefit in patients. No clinical trial could demonstrate that valves were more effective and had fewer complications than occluders. Sabanathan and colleagues reported that 5/8 subjects with endobronchial occluders had improvements in well-being, dyspnea, exercise tolerance, lifestyle, and medication requirements.[10] But there was lack of long-term follow-up. Most clinical trials showed improvement of pulmonary function and exercise tolerance in some subjects in whom atelectasis did not occur.[11,12]

The self-expanding endobronchial occluder (SEEO) was designed by author Liqiang Song and made by Huayishengjie Medical, in Beijing. The SEEO is a novel implantable device designed as a nitinol shape memory wire mesh packed with layers of polyester non-woven fabrics, and is placed by flexible bronchoscopy with local anesthesia. In unpublished dog model studies the placement of SEEO could induce the target lobar area into collapse or atelectasis. This report describes the preliminary human study results with the SEEO to determine feasibility, safety, and efficacy data before proceeding to a larger pivotal clinical trial.

Methods

Subjects

We conducted a preliminary, prospective, nonrandomized, single-center longitudinal cohort study. Twenty-three subjects with severe heterogeneous emphysema were recruited according to visiting sequence and inclusion and exclusion criteria used by Wan et al[13] (Table 1). They underwent BLVR between August and December 2006, and received follow-up visits for 36 months. All subjects had severe dyspnea, with Borg scores ≥ 5.0 on exertion, despite medical treatment before procedure, and accepted examinations, including baseline physiologic, radiologic, and quality-of-life testing. The distribution of emphysema was heterogeneous, as seen by computed tomography (CT)

QUICK LOOK

Current knowledge

Lung-volume-reduction surgery for emphysema improves lung function and quality of life, but the postoperative complications can be severe and expensive, so non-surgical methods such as bronchial occlusion are being studied.

What this paper contributes to our knowledge

In patients with COPD, self-expanding endobronchial occluders significantly improved 6-min walk distance, dyspnea, BODE (body mass index, air-flow obstruction, dyspnea, exercise capacity) index, and quality of life, but the improvements persisted long-term in a minority of patients.

and ventilation-perfusion scintigraphy. Each subject had full pulmonary function tests, arterial blood gas measurements, transthoracic echocardiography, 6-min walk test, dyspnea score, and BODE (body mass index, air-flow obstruction, dyspnea, and exercise capacity) index. Quality of life was assessed with the St George's Respiratory Questionnaire (SGRQ). All the tests were on the same day for each subject, and met American Thoracic Society criteria. The study was approved by the Xijing Hospital ethics committee, and all subjects provided informed written consent for the procedures, data collection, and participation in the clinical trial.

Materials

The SEEO is an implantable device designed for placement in the segmental or subsegmental bronchi by means of flexible bronchoscopy. Each occluder is made of a nitinol wire mesh that is shaped into a stacked-discuses shape with 3 collars to secure the occluder in the target airway, with several layers of polyester fabric inserts designed to block air flow (Fig. 1). As the occlusion device is implanted, it expends outward and the collars push against the wall of the airway.

Procedure

The procedure was performed in the bronchoscopy laboratory. Subjects were placed supine with the head slightly extended, and underwent local anesthesia and sedation. The target areas for SEEO placement were previously selected on the basis of pulmonary CT scan, and the most affected segments were blocked with valves of appropriate size. A flexible bronchovideoscope (BF-240, Olympus,

Table 1. Inclusion and Exclusion Criteria

Inclusion
   Age 50–80 y
   Symptomatic emphysema diagnosed using clinical and radiologic
      criteria
   Shortness of breath on daily activities, despite maximal medical
      therapy
   Radiologic evidence of heterogeneous disease
Exclusion
   $FEV_1 < 20\%$ of predicted
   $P_{aCO_2} < 55$ mm Hg
   $D_{LCO} < 25\%$ of predicted
   Pulmonary hypertension
   Active pulmonary infection
   Subject will not or cannot comply with follow-up investigations

D_{LCO} = diffusing capacity of the lung for carbon monoxide

Tokyo, Japan) passed through the mouth to reach the target bronchial orifices. A guide wire (0.9 mm external diameter) was threaded through the instrument channel of the bronchoscope into the target bronchus. The bronchoscope was pulled out, but another bronchoscope (BF-P240, Olympus, Tokyo, Japan) passed through the nares to the central airway in order to monitor the procedure. The delivery catheter was advanced over the guide wire to the bronchial orifice, and then the guide wire was removed. Under direct observation with the video bronchoscope, the selected SEEO of appropriate size (4 diameter sizes of 5.0 mm, 6.0 mm, 7.0 mm, and 8.0 mm are available) was advanced to the distal end of the delivery catheter and deployed or retrieved using the delivery cable with screw attachment for the occluders. When the SEEO was conformed to block the target bronchus, it would be released by unscrewing the delivery cable from the device. The delivery catheter and cable were removed, followed by a final visual inspection.
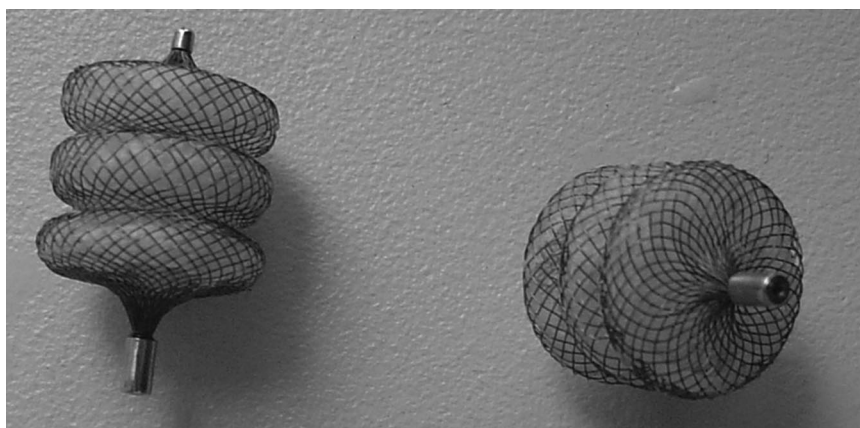
Postoperative Care and Follow-Up

After the procedure, each subject had a chest radiograph taken immediately, and was required to be hospitalized for minimum of 2 days. Subjects received prophylactic antibiotics such as amoxicillin (0.25 g, 3 times/d), clavulanate (0.25 g, 3 times/d), levofloxacin (0.4 g, once a day), as well as inhaled salbutamol postoperatively. All COPD management routines were continued. Subjects returned for follow-up evaluation by the investigators at 1 week, and 1-, 3-, 6-, 12-, 24- and 36-month intervals. The primary end point was safety, as measured by the incidence of migration, erosion, and/or infection related to the occlusion device. Other safety measures included the presence of persistent cough, bronchitis, pneumonia, respiratory failure, hemoptysis requiring intervention, death, and unpredictable adverse events. Participants in the study were invited to contact the investigators at any time after the procedure. Chest CT scan or bronchoscopy were requested at each visit to document the stability of the position of the occlusion device. During follow-up, each subject received an examination consisting of a full pulmonary function test, arterial blood gas measurements, 6-min walk test, dyspnea score assessment, BODE index, SGRQ (for 3 months). Furthermore, all subjects were encouraged to receive appropriate pulmonary rehabilitation.

Four variables were identified prospectively as pilot study measures for efficacy after the procedure: an increase in FEV_1 of $\geq 15\%$, an increase in 6-min walk distance of $\geq 15\%$, a decrease in dyspnea score of ≥ 1, or an improvement in SGRQ total score of > 4 units. These thresholds for minimal clinically important differences were based on published literature.[13]

Statistical Analysis

All descriptive statistics are expressed as mean $\pm$ SD for continuous variables, and as median (range) for ordinal

Fig. 1. The self-expanding endobronchial occluder.

Table 2. Baseline Data of Subjects*

	(mean ± SD)	(range)	Percent of Predicted (mean ± SD)
Age, y	66.57 ± 5.38	58–75	
pH	7.39 ± 0.05	7.31–7.43	
P_{aO_2}, mm Hg	64.14 ± 10.90	56.00–87.2	
P_{aCO_2}, mm Hg	38.50 ± 6.62	28.00–47.33	
FEV_1, L	0.98 ± 0.31	0.56–1.32	35.23 ± 11.23
FVC, L	2.33 ± 0.56	1.63–2.87	66.78 ± 15.50
FEV_1/FVC, %	43.15 ± 12.27	28.04–60.68	54.00 ± 15.34
RV, L	4.13 ± 1.30	2.39–6.24	176.04 ± 44.72
TLC, L	6.36 ± 0.90	4.75–7.20	112.02 ± 13.64
RV/TLC, %	60.00 ± 9.42	50.31–75.00	155.0 ± 23.56
D_{LCO}, mmol/ min/mm Hg	18.59 ± 6.56	10.45–25.86	61.35 ± 18.37
6MWD, m	388 ± 105.05	186–602	
Dyspnea score	3.32 ± 0.67	2–4	
BODE index	5.48 ± 1.62	2–8	
SGRQ total score	63.59 ± 7.00	50–83	

* 20 male, 3 female
RV = residual volume
TLC = total lung capacity
D_{LCO} = diffusing capacity of the lung for carbon monoxide
6MWD = 6-min walk distance
BODE = body mass index, air-flow obstruction, dyspnea, and exercise capacity
SGRQ = St George's Respiratory Questionnaire

data. Paired 2-tailed *t* tests were used to analyze quantitative continuous variables, comparing the means for the groups. The Friedman test and the Wilcoxon rank-sum test were used for ordinal variables. Bonferroni correction was used to adjust the observed significance level when multiple comparisons of the means were made. Analyses were done with statistics software (SAS 9.1.3, SAS Institute, Cary, North Carolina). *P* values were calculated with variance analysis, with $P < .05$ judged significant.

Results

Clinical Characteristics

In the preliminary study a total of 23 subjects underwent the procedure described previously from August to December 2006 (Table 2). All SEEOs were implanted unilaterally in the segmental or subsegmental airways previously selected. Only one lobe was involved in each subject, and the target airways were located in the center of predominantly heterogeneous emphysema rather than indiscriminately in all segments of one lobe. The number of SEEOs inserted for each subject was relative to the individual morbid anatomy. Overall, 58 SEEOs were implanted into 23 lobes (mean 2.52 occluders per subject), in

which there were 8 lower lobes (34.8%) and 15 upper lobes (65.2%). Only 2 entire lobes were blocked, while in the remaining 21 incomplete lobar occlusions were performed (Table 3). There were no procedure-related airway tissue lacerations or deaths associated with the procedure. Most of subjects were discharged at the third day post-procedure. Only 2 subjects stayed in hospital for 7 days, because of moderate cough and expectoration, but experienced no fever or pneumonia.

During the 36 months allowed for follow-up, all subjects finished their return visits according to their individual schedules. Both chest imaging and bronchoscopy views demonstrated fully functioning devices, with no evidence of displacement (Fig. 2). Five subjects experienced complications consistent with mild or moderate (grade 1 or 2 measured by the cough score scale) cough, but without purulent sputum and fever during the immediate postoperative period. These symptoms were gradually ameliorated with the administration of inhaled bronchodilator and anti-tussive agents. Six subjects suffered from lower lobe pneumonia during the follow-up. Three occurred about 12 months after the procedure, and were located in the remaining left lower lobe with the occlusive atelectasis of lateral and posterior basal segments. *Pseudomonas aeruginosa* was isolated in the sputum culture. After antibiotic treatment and local bronchoalveolar lavage under bronchoscopy, the focus of infection was gradually absorbed and left some fibrous scarring. In another case, pneumonia of the infected lobe was different from the target lobe, and also responded to treatment. Other usually reported complications, such as pneumothorax, hemoptysis, and thorax pain, were never observed. Only 2 subjects experienced atelectasis of target lobes, as observed by chest CT scan at 3 months and 12 months post-procedure, respectively (Figs. 3 and 4).

Spirometric and Functional Assessments

For lung function, the FEV_1 in 18 subjects (78.26%) was improved > 15%, compared with baselines. The beginning efficacy time and maximal efficacy time were 5.65 ± 1.51 months and 6.35 ± 3.08 months, respectively. Compared with the maximal FEV_1 (1.17 ± 0.25 L), the baseline FEV_1 (0.94 ± 0.22 L) was improved 24.47% (0.23 L) ($P = .004$) (Table 4) (Fig. 5). In addition, comparing with the baseline, 8 subjects maintained > 10% improvement of FEV_1 at the end time point ($P = .04$). Note that the treatment of COPD from the Toward a Revolution in COPD Health (TORCH) investigators maintained only a 0.029% increase in FEV_1, indicating the positive effect of this endobronchial occluder.[14]

Table 3.   Clinical Characteristics and Complications of Subjects

| Subject Number	Number of Valves	Lobe Valved	Post-Procedure Complications	Outcome
1	2	Left lower	Cough and expectoration immediately, pneumonia at 12 months	Ameliorated, cured
2	2	Right upper	None	
3	3	Left upper	None	
4	2	Left upper	None	
5	3	Right lower	Pneumonia at 8 months	Cured
6	2	Left lower	None	
7	3	Right upper	Cough immediately	Ameliorated
8	3	Right lower	Pneumonia at 8 months	Cured
9	2	Left upper	None	
10	2	Left lower	Pneumonia at 12 months	Cured
11	3	Left upper	None	
12	2	Right upper	None	
13	3	Right lower	None	
14	2	Left lower	Cough and expectoration immediately, pneumonia at 8 months	Cured
15	2	Right upper	None	
16	3	Right upper	Cough immediately	Ameliorated
17	2	Left upper	None	
18	3	Left upper	None	
19	3	Right upper	None	
20	2	Left lower	Pneumonia at 12 months	Cured
21	3	Left upper	None	
22	3	Right upper	Cough immediately	Ameliorated
23	2	Right upper	None	
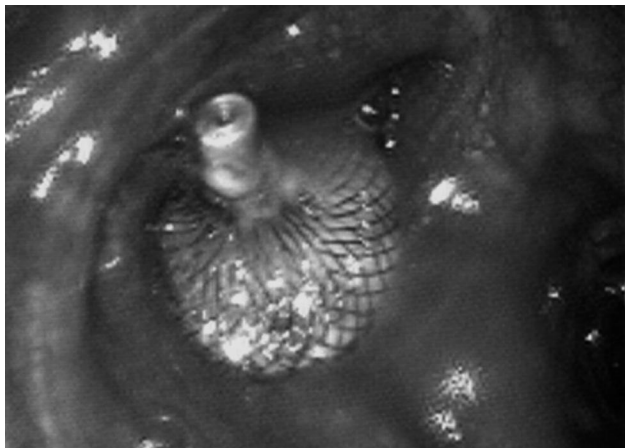
Fig. 2. Bronchoscopic view of a self-expanding endobronchial occluder in bronchus orifice, 1 month post-insertion.

Six-min walk distance showed an improvement of > 15%, compared with baseline, in 22 subjects (95.65%) ($P < .001$). The beginning efficacy time and maximal efficacy time were 3.19 ± 2.69 months and 13.09 ± 5.81 months, respectively. At the end time only 12 subjects (52.17%) kept the improvement. Like-wise, dyspnea score in 22 subjects (95.65%) decreased > 1 point ($P < .001$), and the 2 time-points were 5.36 ± 5.16 months and 7.27 ± 5.06 months, respectively. The dyspnea scores of 7 subjects (30.43%) showed a 1-point decrease at the end of the study ($P = .02$) (see Table 4).

Compared with mean baseline BODE index (6.09 ± 1.59), the values at 3, 6, and 12 months post-BLVR were variously improved: 5.13 ± 1.49 ($P = .03$), 4.74 ± 1.57 ($P = .03$), and 5.00 ± 1.62 ($P = .02$). But BODE index did not continue to show sustained improvements in the remaining time (Fig. 6).

Health-Related Quality of Life Assessments

At 3 months post-BLVR, the SGRQ scores were evaluated. In 20 subjects (86.96%) the total scores were improved > 4 units, compared with baseline, and the beginning efficacy time and maximal efficacy time were 3.27 ± 0.88 months and 12.56 ± 5.11 months, respectively. At the end of the study follow-up, 16 subjects (69.57%) revealed a > 4-unit improvement (see Table 4) ($P = .02$).
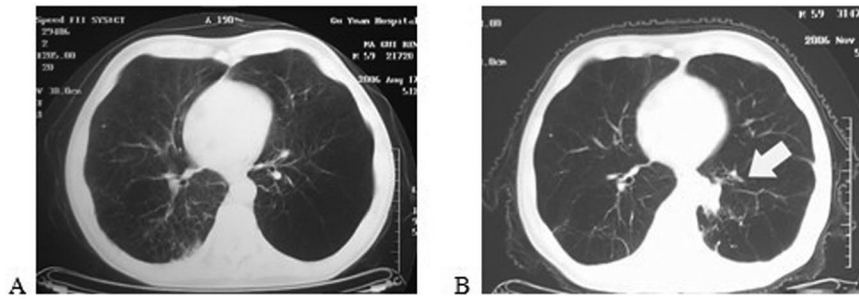
Fig. 3. Computed tomography sections before (left) and 3 months after (right) insertion of self-expanding endobronchial occluders in a 58-year-old male subject with left-lower-lobe-predominant, severe panlobar emphysema. Two self-expanding endobronchial occluders were placed, in the lateral and posterior basal segment bronchi in the left lower lobe, and occlusive atelectasis was visible at 3 months (arrow).
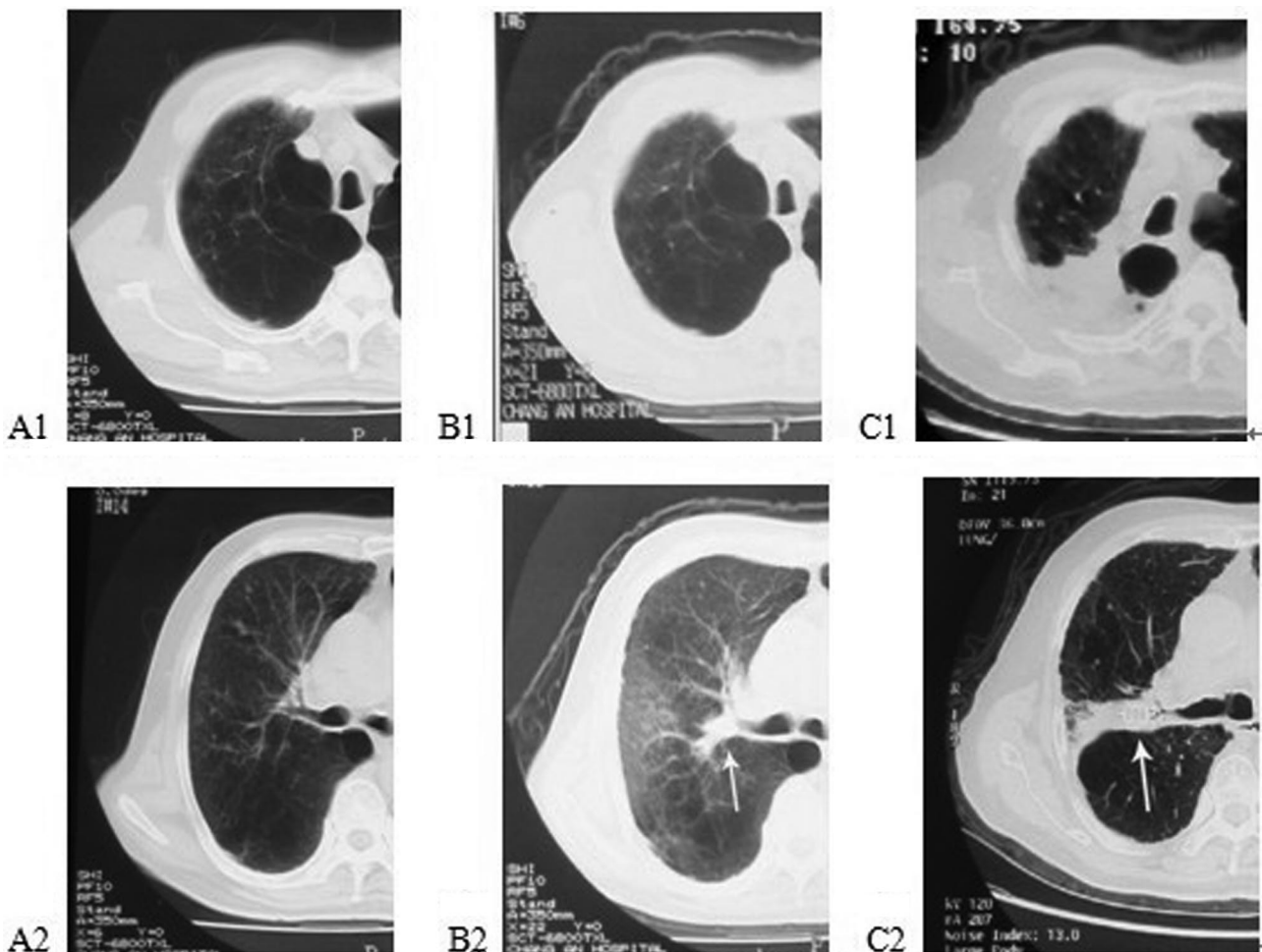

Fig. 4. Computed tomography sections before (A1, A2), 6 months (B1, B2) after, and 12 months (C1, C2) after insertion of self-expanding endobronchial occluders in a 69-year-old male subject with right-upper-lobe-predominant, severe panlobular emphysema. Two self-expanding endobronchial occluders were placed, in an apical segment bronchus (B1, C1) and a posterior segment bronchus (B2, C2) (arrow) in the right upper lobe. Occlusive collapse and atelectasis were visible at 3 months and 12 months.

Discussion

BLVR is characterized by blocking the target airway, and how to design the blocker is still an unresolved problem. SEEO was designed differently from previous airway occluders, including stent and balloon.[10] The results demonstrated that early improvements were statisti-

Table 4.   FEV$_1$, 6MWD, Dyspnea Score, and Health-Related Quality of Life Score

	At Beginning of Improvement	At Maximal Improvement	At End of Follow-up
FEV$_1$			
Improvement ≥ 15%, no. (%)	18 (78.26)	18 (78.26)	5 (21.74)
Time, mean ± SD (range) min	5.65 ± 1.51 (1–12)	6.35 ± 3.08 (1–12)	
Change from baseline, mean ± SD	0.25 ± 0.03*	0.23 ± 0.03*	0.01 ± 0.03
6MWD			
Improvement ≥ 15%, no. (%)	22 (95.65)	22 (95.65)	12 (52.17)
Time, mean ± SD (range) min	3.19 ± 2.69 (0.25–12)	13.09 ± 5.81 (1–12)	
Change from baseline, mean ± SD	67.36 ± 8.58†	104.43 ± 11.86*	62.78 ± 6.94†
Dyspnea score			
Improvement ≥ 1 grade, no. (%)	22 (95.65)	22 (95.65)	7 (30.43)
Time, mean ± SD (range) min	5.36 ± 5.16 (1–24)	7.27 ± 5.06 (1–24)	
Change from baseline, mean ± SD	−1.06 ± 0.02†	−1.38 ± 0.01†	−0.18 ± 0.12
SGRQ total score			
Improvement ≥ 4 units, no. (%)	20 (86.96)	20 (86.96)	16 (69.57)
Time, mean ± SD (range) min	3.27 ± 0.88 (3–6)	12.56 ± 5.11 (3–24)	
Change from baseline, mean ± SD	−8.79 ± 0.11†	−12.69 ± 1.89*	−5.17 ± 1.06†

* $P < .001$.
† $P < .05$.
6MWD = 6-min walk distance
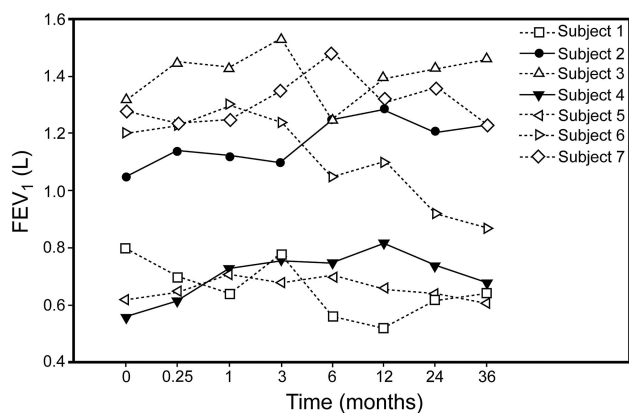SGRQ = St George's Respiratory Questionnaire

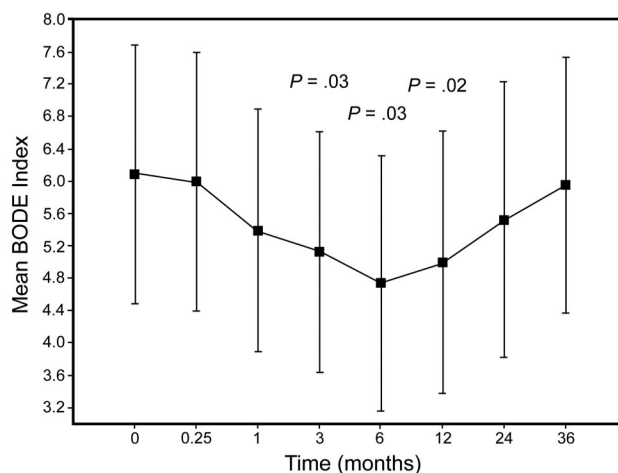Fig. 5. Change in FEV$_1$ in subjects 1–7.

Fig. 6. Change from baseline in mean BODE (body mass index, air-flow obstruction, dyspnea, and exercise capacity) index in all subjects. The whisker bars indicate the full range of values.

cally significant in pulmonary function, 6-min walk distance, dyspnea scores BODE index, and quality of life. Ease of placement and acceptable safety records were all positive.

Placement of SEEO was successful in all desired segments and subsegments with flexible bronchoscope and local anesthesia. With the delivery cable, the device was able to be easily adjusted, removed, or replaced. No displacement was seen under bronchoscopy or by CT scan. Recently, a case showed 2 endobronchial valves migrated from left upper lobe to the lower lobes of left and right, respectively.[15] No severe complications were seen during the 2 days hospital stay post-procedure, so it suggests that

insertion of SEEOs could be performed as an out-patient procedure.

In this study, 5 subjects experienced complications of cough during the immediate postoperative period, without purulent sputum and fever. The symptoms were gradually ameliorated with inhaled bronchodilator. No various relations were found between the bronchospasm incidence and the insertion location, because almost all lobes were involved in previous reports.

Our biggest concern with complications was post-obstructive pneumonia, so we undertook several preventive measures, including selecting stable stage COPD patients, culturing the target area lavage fluid, and providing prophylactic antibiotics. Unfortunately, 6 subjects suffered from lower lobe pneumonia; fortunately, it was not the direct result of the occluder insertion, although one subject had pneumonia located in the left lower lobe adjacent to the post-obstructive atelectasis. The time of occurrence was nearly 1 year after the procedure. Two causes were presumed for the lower lobe pneumonia. First, due to anatomical characteristics, the drainage of secretions in the lower lobe was apt to be inadequate. Second, the inflammation reaction and granulation tissue formation in the target airway might cause stenosis of vicinity orifices.[16] Therefore, we considered that upper lobes would be selected rather than lower lobes, in order to reduce the incidence of post-obstructive pneumonia in BLVR. And LVRS outcomes are usually better in subjects with upper-lobe predominant emphysema than in those with diffuse emphysema.[17] Sciurba reported that the rate of pneumonia in the target lobe in the endobronchial valves group was 4.2% at 12 months.[18] Kotecha reported 5/16 subjects had new microbial organisms isolated after endobronchial valve insertion.[16]

Most of our subjects experienced early improvements in pulmonary function, exercise tolerance, dyspnea score, BODE index, and SQRQ score. But the improvement of pulmonary function was sustained long-term in a minority of subjects. The result was in accordance with the reports from most BLVR studies.[7,18] Although the therapeutic benefits of BLVR also diminish over time due to disease progression and possibly treatment-related acceleration of lung function loss, objective benefit has been observed for years after treatment. This is particularly true for subjects with upper-lobe-predominant emphysema.[12,19,20] By contrast, physiological benefits after LVRS often diminish substantially within months. In general, BLVR responses still appear to be more durable than LVRS.[20]

Conclusions

In conclusion, this is the first detailed report on the long-term outcome of SEEO placement for emphysema treatment. The results demonstrate early significant improvements in pulmonary function, BODE index, and SGRQ score, and acceptable safety, ease of use, and procedural complication rates. But the improvement was maintained long-term in only a minority of subjects. Selecting upper-lobe-predominant emphysema as a target area, selecting a suitable size of SEEO, and inserting the SEEO step by step until atelectasis occurs will improve the safety and efficacy of BLVR. The weakness of the study is the small number of recruited subjects, a single center, and the lack of a control group. The small sample size limits our ability to draw definitive conclusions. Clarification of the occluder role in the management of severe COPD will depend on the results of larger randomized controlled trials.

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