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

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ABSTRCT

Purpose: This article describes the Self-Expanding Endobronchial Occluder (SEEO) as utilized in Bronchoscopic Lung Volume Reduction (BLVR) with a 36 month follow-up procedure.

Methods: 23 Patients with severe emphysema were recruited and underwent flexible bronchoscopic placement of the SEEOs. Outcomes were assessed at 1 week, 1-month, 3-, 6-, 12-, 24- and 36-month intervals including the feasibility, safety and efficacy which contained pulmonary function testing, 6-minute walking distance (6MWD) test, dyspnea grade assessment, BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity) index and St. George Respiratory Questionnaire (SGRQ).

Results: 58 SEEOs were implanted into 23 lobes previously selected. No displacement was found during the follow-up. 5 patients experienced post-operative complications of cough and 6 patients were subjected to lobar pneumonia, which were not located in any of the blocked segments. The FEV_1 in 18 patients were improved by more than 15% compared with baselines ($P<0.001$), and the mean first efficacy time and maximal efficacy time were 5.65±1.51 months and 6.35±3.08 months, respectively. The mean baseline DL_{CO} significantly increased over a 12-month period ($P<0.05$). No significant changes were observed in FVC and RV/TLC. 6MWD test, dyspnea grades and SGRQ total scores were improved in 22 patients over a 24-month periods with a minority of patients continuing to improve until the end of the study. Mean baseline BODE index was improved during

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follow-up but not at the study's conclusion.

Conclusions: The preliminary study demonstrates early significant improvements in pulmonary function, 6MWD test, dyspnea grades, BODE index, Quality-of-life, and ease of placement and acceptable safety post BLVR with SEEOs. But the initial improvements were only maintained long term for a minority of patients.

Key words: Emphysema; Bronchoscopic lung volume reduction; Endobronchial occluder; Pulmonary function; Safety

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of chronic morbidity and mortality throughout the world, characterized by airflow limitation that is not fully reversible[1]. In China, the overall prevalence of COPD was 8.2% (men, 12.4%; women, 5.1%) with stage III (1.7%) and IV (0.4%) in individuals 40 years of age or older, and there are about 1 million deaths and over 5 million disabilities each year mainly caused by COPD[2]. So how to improve the symptoms and life quality of severe COPD patients is an urgent social problem.

None of the existing medications for COPD have 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 of Lung Volume Reduction Surgery (LVRS) has shown promise and reached later-stage clinical trials[5, 6]. Most of BLVR methods attempt to induce atelectasis by the implantation of endobronchial devices including bronchial occluder, bronchial valves, glues and bio-modulators. In all clinic trials to date, most patients had been 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 lung and reducing the potential for post-obstructive pneumonia.

However, no particular valve has proven to be consistently effective in generating

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

The Self-Expanding Endobronchial Occluder (SEEO) was designed by Dr. Liqiang Song and made by Huayishengjie Medical Inc in Beijing. 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.

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Methods

Patients

We conducted a preliminary, prospective, nonrandomized, single-center longitudinal cohort study. 23 patients with severe heterogenous emphysema were recruited according to visiting sequence and inclusion and exclusion criteria used by Wan [13](Table 1). They underwent BLVR between August to December 2006 and received follow-up visits for 36 months. All patients had severe dyspnea with Brog 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 tomographic (CT) and ventilation/perfusion scintigraphy. Each patient received full pulmonary function tests including arterial blood gas measurements, transthoracic echocardiography, 6-minute walking distance (6MWD) test, dyspnea grade assessment and BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity) index. Quality-of-life was assessed by using the St George Respiratory Questionnaire (SGRQ).All the tests should be finished at the same day for each patients and met according to the instruction of ATS criteria. The study was approved by the Xijing Hospital Ethics Committee and all patients 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

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Nitinol wire mesh that is shaped into a stacked-discuses shape with three collars to secure the occluder in the target airway, with several layers of polyester fabric inserts designed to block airflow (Figure 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. Patients 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, Japan) passed through the mouth to reach the target bronchial orifices. A guide wire (0.035-inch external diameter) was threaded through the instrument channel of bronchoscope into the target bronchus. The bronchoscope was pulled out but another bronchoscope (BF-P240, Olympus, Japan) passed through the nares to the central airway in order to monitor the procedure. Delivery catheter was advanced over the guide wire to the bronchial orifices 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.

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Postoperative care and follow-up

After the procedure, each patient had a chest radiograph taken immediately and were required to be hospitalized for minimum of 2 days. Patients received prophylactic antibiotics such as amoxicillin (0.25g 3times/day), clavulanate(0.25g 3times/day), levofloxacin(0.4g once a day) as well as inhaled salbutamol postoperatively. All COPD management routines were continued. Patients returned for follow-up evaluation by the investigators at 1 week, 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 or 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 procedure. Chest CT scan or bronchosopy were requested at each visit to document the stability of the position of the occlusion device. During follow-up, each patient received an examination consisting of a full pulmonary function test, arterial blood gas measurements, 6MWD test, dyspnea grade assessment, BODE index, the SGRQ (for 3 months). Furthermore, all patients were encouraged receive appropriate pulmonary rehabilitation.

Four variables were identified prospectively as pilot study measures for efficacy after the procedure: an increase in FEV_1 of 15% or greater, an increase of 6MWD of 15% or greater, a decrease of dyspnea grade of one grade or greater, or an improvement in SGRQ total score of more than 4 units. These thresholds for minimal

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clinically important differences were based on published literature [13].

Statistical analysis

All descriptive statistics were expressed as mean ± SD for continuous variables and as median (range) for ordinal data. Paired 2-tailed *t tests* were used to analyze quantitative continuous variables comparing the means for the group. 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 SAS version 9.1.3. P values were calculated with variance analysis, with $P < 0.05$ judged significant.

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Results

Clinical characteristics

In the preliminary study, a total of 23 patients 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 patient, 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 patient was relative to the individual morbid anatomy. Overall, 58 SEEOs were implanted into 23 lobes (mean 2.51 occluders per patient), 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 was no procedure-related airway tissue lacerations or deaths associated with the procedure. Most of patients were discharged at the third day postprocedure. Only 2 patients 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 patients finished their return-visit according to their individual schedules. Both chest imaging and bronchoscopy views demonstrated fully functioning devices with no evidence of displacement (Figure 2). 5 patients experienced complications consistent with mild or moderate (grade 1 or 2 measured by cough score scale) cough but without purulent sputum and fever during the immediate postoperative period. These symptoms were gradually ameliorated with

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the administration of inhaling bronchodilator and anti-tussive agents. 6 patients suffered from lower lobe pneumonia during the follow-up. Three occurred about 12 months after the procedure, and was located in the remaining left lower lobe with the occlusive atelectasis of lateral and posterior basal segements. *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 scaring. In another case, pneumonia of the infected lobe was different from the target lobe and also responded to treatment. Other complications usually reported such as pneumothorax, hemoptysis, and thorax pain were never observed. Only 2 patients experienced atelectasis of target lobes as observed by chest CT scan at 3 months and 12 months postprocedure, respectively (Figure 3,4).

Spirometric and functional assessments

For lung function, the FEV_1 in 18 patients (78.26%) were improved more than 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±0.25L), the baseline FEV_1 (0.94±0.22L) was improved 24.47% （0.23L）(P=0.0039) (Table 4) (Figure 5). In addition, comparing with the baseline, 8 patients maitained more than 10% improvement of FEV1 at the end time point (P=0.037). While the treatment of COPD from the Torch investigators maintained only 0.029% increase in FEV1, indicating the positive effection of this endobronchial occluder [14].

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6MWD test experienced an improvement with more than 15% compared with baseline in 22 patients (95.65%) (P<0.001). 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 patients (52.17%) kept the improvement. Likewise, dyspnea scores in 22 patients (95.65%) were decreased more than one grade (P<0.001), and the two time-points were 5.36±5.16 months and 7.27±5.06 months, respectively. The dyspnea grades of 7 patients (30.43%) showed 1 grade decrease at the end of the study (P<0.05) (Table 4).

Compared with mean baseline BODE index (6.09±1.59) the values in 3, 6, 12 months post BLVR were variously improved (5.13±1.49, P = 0.03; 4.74±1.57, P = 0.03; 5.00±1.62, P = 0.02). But BODE index did not continue to show sustained improvements in the remaining time (Figure 6).

Health-related quality of life assessments

At 3 months post BLVR, the SGRQ of patients were evaluated. In 20 patients (86.96%) the total scores were improved more than 4 units compared with baseline, and the beginning efficacy time and maximal efficacy time were 3.27±0.88 months and 12.56±5.11months, respectively. At the end of the study at follow-up, 16 patients (69.57%) revealed more than 4 units improvement (Table 4) (P<0.05).

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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 statistically significant in pulmonary function, 6MWD test, dyspnea grades BODE, quality-of-life, besides, 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 devise was able to be easily adjusted, removed, or replaced. No displacement was seen under bronchoscopy or by CT scan. Recently a case showed two 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 postprocedure, so it suggested that insertion of SEEOs was likely to be performed as an outpatient procedure.

In this study, 5 patients experienced complications of cough during the immediate postoperative period without purulent sputum and fever. The symptom could be gradually ameliorated with inhaling bronchodilator. No various relations were found between the bronchospam incidence and the inserted location because almost all lobes were involved in previous reports.

Our biggest concern with complication was post-obstructive pneumonia. So they were given several preventive measures including selecting stable stage COPD

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patients, culturing the target area lavage-fluid and providing prophylactic antibiotics. Unfortunately 6 patients suffered from lower lobe pneumonia. But fortunately, it was not the direct result of the occluder insertion although one of patients had pneumonia located in the left lower lobe adjacent to the postobstructive atelectasis. The time of occurrence was nearly 1 year after the procedure. Two causes were presumed for the lower lobe pneumonia. First, the drainage of secretion in lower lobe was apt to be inadequate with anatomic characteristic. Second, the inflammation reaction and granulation tissue formation in target airway might cause the stenosis of vicinity orifice[16]. Therefore, we considered that upper lobes would rather be selected than lower lobes in order to reduce the incidence of post-obstructive pneumonia in BLVR. And LVRS outcomes are usually better in patients with upper-lobe predominant emphysema than in those with diffuse emphysema[17]. Sciurba reported the rate of pneumonia in the target lobe in the EBVs group was 4.2% at 12 months[7]. Kotecha reported 5/16 patients had new microbial organisms isolated after EBVs insertion[16].

The data from this study indicated that most patients experienced early improvements in part of pulmonary function, exercise tolerance, dyspnea scores, BODE and HRQOL. But the improvement of pulmonary function was sustained long-term in a minority of patients. The result was accordant to the reports from most of 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 patients with upper lobe–predominant emphysema[12,1920]. By

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contrast, physiological benefits after LVRS often diminish substantially within months. In general, BLVR responses still appear to be more durable than LVRS[20].

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 and HRQL and acceptable safety, ease of use and procedural complication rates. But the improvement was only maintained long term in a minority of patients. Selecting upper lobe–predominant emphysema as a target area, selecting suitable size of SEEO, and inserting SEEO step by step until atelectasis occurs will improve the safety and efficacy of BLVR. The weakness of the study is fewer numbers of recruited patients, a single center, and a 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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Legend

Figure 1. Self-Expanding Endobronchial Occluder appearance

Figure 2. Bronchoscopic view of one SEEO inserted in bronchus orifice at 1 month postprocedure

Figure 3. CT sections before (A) and 3 months (B) after occluders insertion in a 58-year-old male patient with severe panlobular emphysema predominant in the left lower lobe. Two SEEOs were placed in the lateral and posterior basal segements bronchi in left lower lobe and the occlusive atelectasis was visible at 3 months (arrow).

Figure 4. CT sections before (A1,A2), 6 months (B1,B2) and 12 months (C1,C2) after occluders insertion in a 69-year-old male patient with severe panlobular emphysema predominant in the right upper lobe. Two SEEOs were placed in apical segement bronchus and posterior segement bronchus (arrow) in right upper lobe, respectively, and the occlusive collapse and atelectasis were visible at 3 months and 12 months, respectively.

Figure 5. Changes of FEV1 in 7 patients (Patient no. 1-7 in Table 4) with follow-up time.

Figure 6. Changes in mean BODE index in all patients with follow-up time

(*compared with mean baseline BODE index)

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Table 1- Inclusion and Exclusion Criteria

Inclusion
Age 50 to 80 yr
Symptomatic emphysema diagnosed using clinical and radiologic criteria
Shortness of breath on daily activities despite maximal medical therapy
Radiologic evidence of heterogeneous disease
Exclusion
FEV1 < 20% of predicted value
$Paco_2$ < 55 mm Hg
DLco <25% of predicted value
Pulmonary hypertension
Active pulmonary infection
Patient will not or cannot comply with follow-up investigations

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Table 2. Baseline data of patients (n=23)

	Mean±SD	Range	Percent predicted(mean±SD)
Age (y)	66.57±5.38	58-75	
Male/female sex	20/3		
PH	7.39±0.05	7.31-7.43	-
PaO_2 (mmHg)	64.14±10.90	56.00-87.2	-
$PaCO_2$ (mmHg)	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
DL_{CO} (mmol/min/mmHg)	18.59±6.56	10.45-25.86	61.35±18.37
6MWD (m)	388±105.05	186-602	-
Dsypnea Grade	3.32±0.67	2-4	-
BODE index	5.48±1.62	2-8	-
SGRQ total scores	63.59±7.00	50-83	-

SD, Standard deviation; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *RV*, residual volume; *TLC*, total lung capacity; *DL_{CO}*, diffusing capacity of lung for carbon monoxide; *6MWD*, 6-minute walk distance; *BODE*, (body mass index, airflow obstruction, dyspnea, and exercise capacity); *SGRQ*, St George's Respiratory Questionaire

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Table 3. Clinical characteristics and complications of patients

Patient no.	No. valves	Position of valves	Complications of postprocedure		
			Diagnosis	Time	Outcome
1	2	LLL	Cough, expectoration; Pneumonia	Immediately 12 months	Ameliorated Cured
2	2	RUL	None	-	-
3	3	LUL	None	-	-
4	2	LUL	None	-	-
5	3	RLL	Pneumonia	8 months	Cured
6	2	LLL	None	-	-
7	3	RUL	Cough	Instant	Ameliorated
8	3	RLL	Pneumonia	8 months	Cured
9	2	LUL	None	-	-
10	2	LLL	Pneumonia	12 months	Cured
11	3	LUL	None	-	-
12	2	RUL	None	-	-
13	3	RLL	None	-	-
14	2	LLL	Cough, expectoration; Pneumonia	8 months	Cured
15	2	RUL	None	-	-

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16	3	RUL	Cough	Instant	Ameliorated
17	2	LUL	None	-	-
18	3	LUL	None	-	-
19	3	RUL	None	-	-
20	2	LLL	Pneumonia	12 months	Cured
21	3	LUL	None	-	-
22	3	RUL	Cough	Instant	Ameliorated
23	2	RUL	None	-	-

RLL, Right lower lobe; *RUL,* right upper lobe; *LUL,* left upper lobe; *RLL,* right lower lobe; *LLL*, Left lower lobe

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Table 4. FEV1, 6MWD, Dyspnea Grade and Health-related quality-of-life improvement and proportion responding

	Time of beginning improvement	Time of maximal improvement	The end time of follow up
FEV1			
Proportion with improvement≥15%	18(78.26%)	18(78.26%)	5(21.74%)
Average time/Range (m)	5.65±1.51/1-12	6.35±3.08/1-12	-/-
change compared with baseline	0.25±0.03**	0.23±0.03**	0.01±0.03
6MWD			
Proportion with improvement≥15%	22(95.65%)	22(95.65%)	12(52.17%)
Average time/Range (m)	3.19±2.69/0.25-12	13.09±5.81/1-12	-/-
Change compared with baseline	67.36±8.58*	104.43±11.86**	62.78±6.94*
Dyspnea Grade			
Proportion with improvement≥1 grade	22(95.65%)	22(95.65%)	7(30.43%)
Average time/Range (m)	5.36±5.16/1-24	7.27±5.06/1-24	-/-
Change compared with baseline	-1.06±0.02*	-1.38±0.01*	-0.18±0.12
SGRQ total scores			
Proportion with improvement≥4 units	20(86.96%)	20(86.96%)	16(69.57%)
Average time/Range (m)	3.27±0.88/3-6	12.56±5.11/3-24	-/-
Change compared with baseline	-8.79±0.11*	-12.69±1.89**	-5.17±1.06*

FEV_1, forced expiratory volume in 1 second; 6MWD, 6-minute walk distance; SGRQ, St George's Respiratory Questionaire; N/A, not available.** P<0.001, * P<0.05,

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significant difference was obseved

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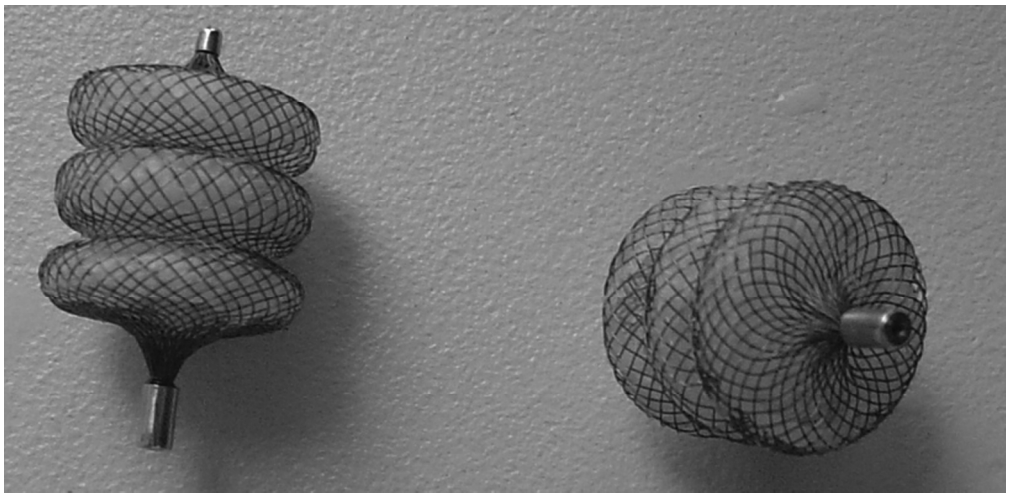

203x99mm (300 x 300 DPI)

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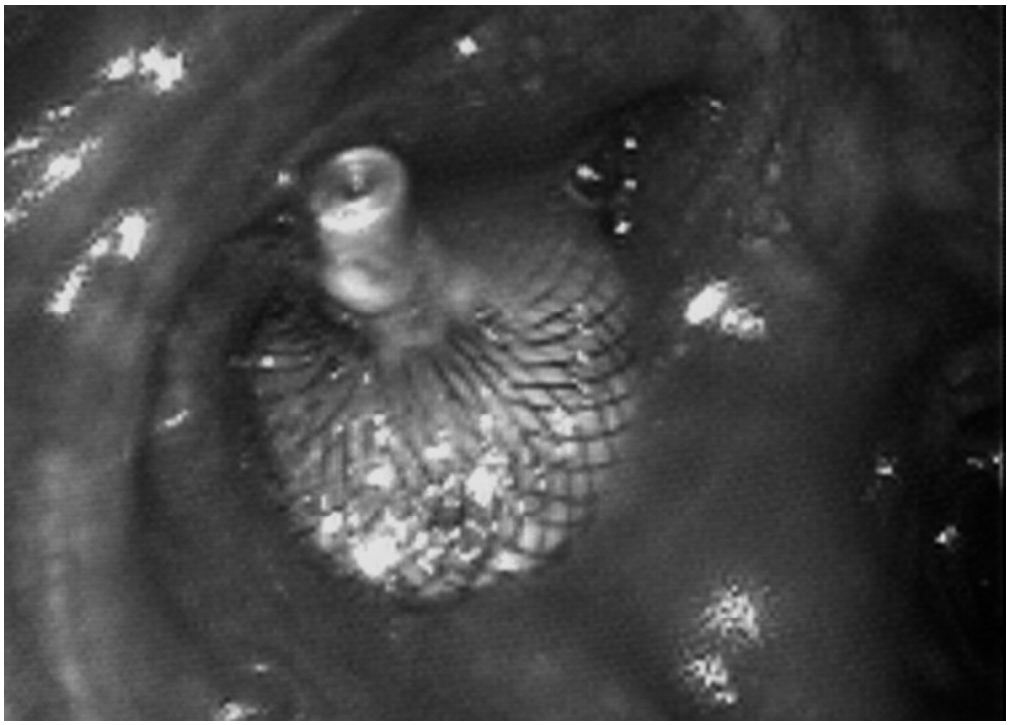

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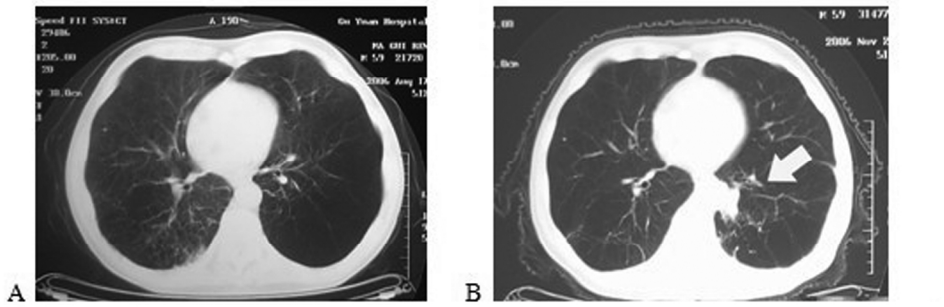

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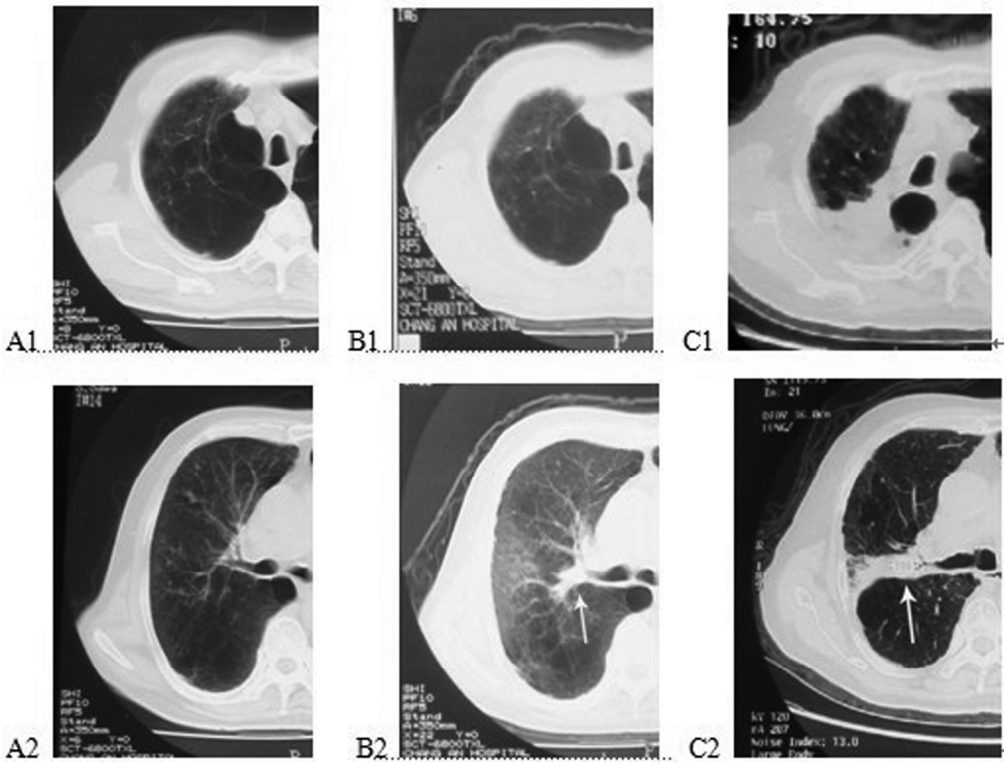

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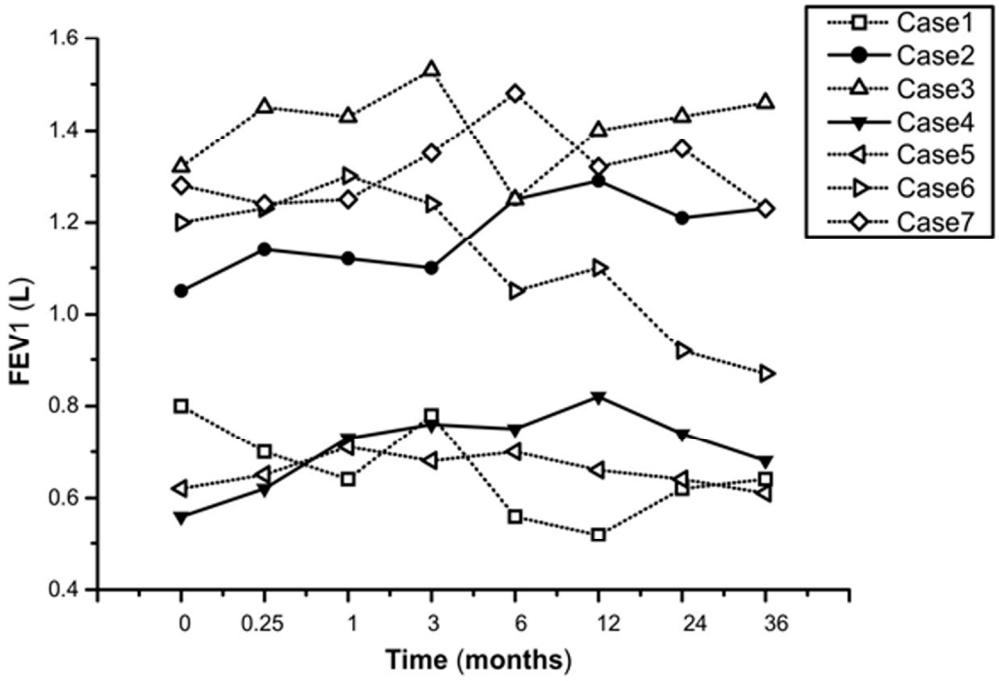

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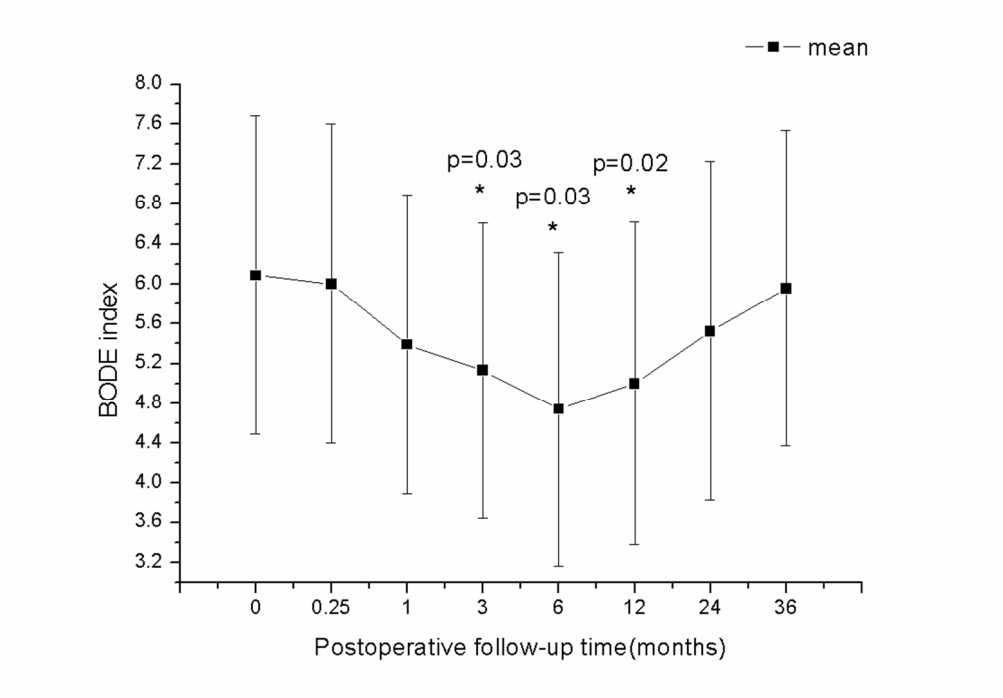

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