

# Status of and prospects for bronchoscopic lung volume reduction for patients with severe emphysema

Hang Yu, Lijie Wang, Zhen Wu, Zhen Yang\*

Department of Respiratory Medicine, Chinese PLA General Hospital, Beijing, China.

## Summary

**Bronchoscopic lung volume reduction (BLVR) is a minimally invasive treatment for severe emphysema, providing treatment options for patients who are unable to undergo lung volume reduction surgery (LVRS) or lung transplantation. Current BLVR techniques include bronchoscopic volume reduction with valve implants, use of a lung volume reduction coil (LVRC), bronchoscopic thermal vapor ablation (BTVA), biological lung volume reduction (BioLVR), and use of airway bypass stents (ABS). To date, several randomized controlled trials of these bronchoscopic therapies have been conducted in patients with emphysema, and bronchoscopic volume reduction with valve implants remains the best approach thus far. Recent studies indicate that BLVR may be of great value in improving lung function, exercise capacity, and quality of life and that BLVR has the potential to replace conventional surgery for patients with severe emphysema. Optimal patient selection and the proper selection of the BLVR technique in accordance with patient characteristics are crucial to the success of BLVR. More multicenter, prospective, randomized controlled trials need to be conducted in the future to optimize the current selection strategy and evaluate the safety, efficiency, and long-term benefit of BLVR techniques.**

**Keywords:** Bronchoscopic lung volume reduction, chronic obstructive pulmonary disease, emphysema, endobronchial valve

## 1. Introduction

Chronic obstructive pulmonary disease (COPD) is a severe chronic respiratory disease characterized by progressive development and airflow limitation that is not fully reversible, and COPD seriously affecting the mobility and quality of life of patients (1). COPD is a serious global public health problem because of its high mortality and high morbidity; globally, COPD patients numbered about 65 million in 2005 and COPD resulted in about 300 million deaths. By 2020, this ailment will be among the world's top three major causes of death (2,3). Emphysema is a key pathology and type of COPD. Chronic airway inflammation causes a reduction in lung tissue elasticity; without

that elasticity, the bronchial and alveolar walls are destroyed (emphysema), leading to airway collapse, hyperinflation, and gas trapping (4). When emphysema is severe, traditional medical treatments include bronchodilators and anti-inflammatory drugs are ineffective; patients suffer decreased lung function and a severely diminished quality of life, and they eventually die from respiratory failure.

Surgery to treat severe COPD and emphysema has been performed for many years, including lung volume reduction surgery (LVRS) and lung transplantation. In 1957, Mueller first proposed the use of LVRS to treat emphysema (5). LVRS involves removing tissue affected by emphysema, thereby reducing ineffective ventilation and improving lung ventilation while the remaining lung enlarges. Pulmonary vascular resistance decreased and right ventricular function improves. Thus, LVRS is effective in reducing difficulty breathing and improving lung function and quality of life (6). The National Emphysema Treatment Trial (NETT) found that LVRS was effective, but only did patients with low exercise capacity and predominantly upper

Released online in J-STAGE as advance publication September 5, 2016.

\*Address correspondence to:

Dr. Zhen Yang, Department of Respiratory Medicine, Chinese PLA General Hospital, Beijing 100853, China.  
E-mail: yztogetyou@163.com

lobe emphysema benefit from LVRS (7). NETT also found that the wide use of LVRS was limited in clinical contexts because of the physical condition the patient had to be in, surgical trauma, a postoperative mortality rate of up to 7.9% in the next 90 days, an incidence of pulmonary complications as high as 29.8%, and an incidence of cardiovascular complications as high as 20.8%. Whether lung transplantation may improve lung function, pulmonary activity, quality of life, and long-term survival for patients with emphysema appears inconclusive, and such an option cannot be widely promoted due to the vast shortage of donors, surgical trauma, major problems after transplant rejection, and infection (8,9). Therefore, surgery has limited ability to meet clinical needs, and a new, minimally invasive, and effective treatment is needed to eliminate the bottleneck limiting current techniques and approaches.

Bronchoscopic lung volume reduction (BLVR) originated in 2001 and developed rapidly afterwards as a new option to treat severe emphysema (10). BLVR techniques are categorized as blocking and non-blocking techniques and their use is based on the type of emphysema and interlobular collateral ventilation. Blocking BLVR involves reversible implantation of one-way valves, while non-blocking involves use of a lung volume reduction coil (LVRC), bronchoscopic thermal vapor ablation (BTVA), biological lung volume reduction (BioLVR), or use of airway bypass stents (ABS). This paper aims to provide an overview of the status of and progress in BLVR research according to the current literature. The latest and most investigated BLVR techniques are summarized in Table 1.

## 2. Blocking BLVR – Valve Implantation

### 2.1. Endobronchial valves and intrabronchial valves

One-way valve implantation for treatment of severe emphysema was first reported in 2003 (11). Currently, two types of valves are used, the endobronchial valves (EBVs) (Zephyr; Pulmonx, Inc., Neuchatel, Switzerland) and intrabronchial valves (IBVs) (Spiration; Olympus, Tokyo, Japan). A one-way valve is held in place by a coated (a silicone membrane for EBVs and polyurethane film for IBVs) self-expanding NiTi retainer. The two types of valve function differently because of their structure. An IBV has anchors that hold an umbrella-shaped valve in place in an airway. The valve closes to allow trapped air and mucus to escape the damaged lung and it opens to block breath from entering the damaged lung. Since the IBV has to be anchored, it depends on the wall of the airway. An EBV is a duckbill valve that fits snugly in an airway with the bill pointed away from the damaged lung. Air and mucus can pass through the valve to escape the damaged lung during expiration, but the close of the valve during inspiration blocks air from entering the

damaged lung. In contrast to the IBV, the EBV depends less on the airway wall. Either valve is placed using bronchoscopy to prevent gas from entering during inhalation while not affecting the exhalation of gas and secretions. This reduces lung hyperinflation, resulting in a reduction in lung volume, while the blocked portion undergoes relatively normal lung tissue recruitment. Valve implantation is a reversible procedure, and either type of valve can be removed at any time using a bronchoscope.

EBVs are the most widely studied and widely used valves. Early studies were based on observational studies and indicated that EBV implantation was safe, but most studies have found that EBV implantation has little benefit (11-17). A series of early studies indicated that EBV implantation substantially benefited patients in whom the target lobe collapsed and in whom target lung volume reduction (TLVR) was achieved, but TLVR was achieved in only 24.9% of patients (11-15). Post-procedure quality of life and exercise capacity improved to some extent for patients with no significant collapse of the target lobe, the difference was not statistically significant (16,17). Although the target lobe does not collapse, EBV implantation reduces physiological dead space and it improves the efficiency of ventilation; increased ventilation allows more air to healthy lungs and reduces dynamic hyperinflation, so patients receive a slight benefit. These early studies proved that collapse of the target lung is the ultimate goal of EBV implantation.

In those early studies, EBVs were usually implanted in one lung or both lungs. Wan *et al.* (17) found that patients undergoing EBV implantation in one lung had more benefits than those receiving implants in both lungs. Unilateral implantation differed significantly from LVRS, which requires treatment of both lungs to have an obvious benefit. Theoretically, expansion of the opposite lung can lead to collapse of the target lung after unilateral implantation of an EBV. In the study by Wan *et al.*, post-operative complications increased when both lungs were treated. In light of these findings, EBV implantation is almost always performed unilaterally.

The Endobronchial Valve for Emphysema Palliation Trial, or VENT, was the first and largest randomized controlled trial (RCT) of valve implantation to treat emphysema; the trial was conducted separately in the US and Europe (18,19). In US VENT study by Sciruba *et al.*, an EBV was implanted in 214 patients with emphysema, and results indicated that the forced expiratory volume in 1 second (FEV<sub>1</sub>) increased by 4.3% over the previous procedure in 6 months, compared to a decrease of 2.5% in the control group ( $p = 0.005$ ). Similar differences were observed in the 6-minute walk test (6MWT) and health-related quality of life measured with the St. George's Respiratory Questionnaire (SGRQ), and the modified Medical Research Council (mMRC) Dyspnea scale (18). In the

European VENT study, respiratory symptom scores on the SGRQ also improved significantly after 6 months for patients receiving an EBV in comparison to the control group (19). Results of the VENT study indicated that EBV implantation is effective in treating patients with severe emphysema, but the clinical improvements were not significant. In order to improve the effectiveness of EBV implantation, a retrospective study of the VENT results and a series of studies examined the characteristics of patients receiving EBVs and those studies described a series of predictive factors as will now be described.

## 2.2. Factors predicting the success of valve treatment

### 2.2.1. TLVR

A retrospective study of the VENT results indicated that there was a significant correlation between TLVR and the success of EBV implantation (20). Improvements in the BODE index (more than 1 point) were observed in 67% of patients with a TLVR > 50%, 37% of patients with a TLVR of 20-50%, and 41% of patients with a TLVR < 20% ( $p = 0.011$  for intergroup differences). The study also indicated that a TLVR of more than 350 mL was an independent predictor of the success of EBV implantation. A long-term-survival study ( $n = 19$ ) indicated that 5 patients who developed atelectasis in the target lobe survived 6 years after EBV implantation while 8 of 14 patients with no atelectasis died (21). Another study ( $n = 33$ ) indicated that patients with atelectasis in the target lobe after EBV implantation had a better long-term survival (22).

The importance of TLVR in IBV implantation has been indicated. Unlike complete occlusion of the target lobe with an implanted EBV, IBV implantation involves incomplete occlusion of more than one lobe in bilateral lungs in the hopes of achieving TLVR with no increase in post-procedure complications. However, two multicenter studies of IBV implantation found that the volume of the patient's target lobe and lung function decreased slightly and exercise capability did not improve significantly after IBV implantation (23,24). An RCT involving 277 patients found that incomplete bilateral occlusion did not achieve a satisfactory TLVR (TLVR is only about 200 mL), and the treatment group displayed no significant improvement according to their SGRQ scores (25). Eberhardt *et al.* compared the use of implanted IBVs in complete unilateral occlusion and incomplete bilateral occlusion (26). In 7 of 11 patients, complete occlusion resulted in collapse of the target lobe; in 11 patients with incomplete occlusion, none had atelectasis. Lung function, exercise capability, and quality of life after IBV implantation differed significantly in the two groups of patients. Therefore, incomplete bilateral occlusion with an implanted IBV has been abandoned, and new strategies for IBV

implantation need to be developed for the technique to be effective.

### 2.2.2. Fissure integrity

In addition to the surgical technique and anatomical abnormalities, collateral channels of ventilation can affect the collapse of the target lobe. Both normal individuals and patients with emphysema have interalveolar channels (pores of Kohn), bronchiole-alveolar channels (canals of Lambert), and interbronchiolar channels (channels of Martin). The existence of these channels means that an EBV must block all segments of the target lobe (27-30). Interlobular collateral ventilation is main factor influencing TLVR and determining the success of EBV implantation. This collateral ventilation is the inevitable result of emphysema damaging the interlobular fissure. Therefore, integrity of the interlobular fissure is likely to be a predictor of the success of EBV implantation.

A retrospective analysis of the VENT results confirmed this theory. Six months after EBV implantation, patients with complete interlobular fissures (defined as more than 90% completeness of the fissure between the target and adjacent lobes on the cross-sectional, sagittal, or coronal plane on MDCT) had a significant improvement in lung function (19). Recently, an RCT known as the BeLieVeR-HIFi study implanted valves in patients with intact interlobular fissures on CT ( $n = 25$ ) and the study compared those patients to a control group who received sham valve implantation ( $n = 25$ ) (31). After 3 months, the FEV<sub>1</sub> in the group receiving a valve increased by a mean of 24.8% (median 8.77%) compared to 3.9% (median 2.88%) in the control group ( $p = 0.0326$ ). A clinically significant improvement (improvement in FEV<sub>1</sub>  $\geq 15\%$ ) was noted in 39% of patients and in only 4% of the control group ( $p = 0.0044$ ).

### 2.2.3. Direct measurement of collateral ventilation

Current methods for the assessment of fissure integrity are mainly based on visual assessment by imaging experts using high-resolution reconstructed CT images (18,19,31). The assessments are heavily influenced by the level of experience of the experts and they are highly subjective, and often there is disagreement between imaging experts (32). With the development of computer technology, automated analysis can improve the efficiency and accuracy of inspections of the interlobular fissure, but it still cannot replace the role of imaging experts (33,34). In the BeLieVeR-HIFi study, 4 patients with a complete interlobular fissure according to imaging experts failed to benefit from EBV implantation (31).

The Chartis Pulmonary Assessment System (Pulmonx, Inc., Neuchatel, Switzerland) is a direct method to determine whether interlobular collateral ventilation (CV) exists in the target lobe. A catheter with a balloon at its tip is placed in the bronchus of

**Table 1. Summary of reported trials on bronchoscopic lung volume reduction**

Device/year (Ref.)	Design	No. of patients treated	Emphysema phenotype: hetero, homo, or both	Procedure unilateral or bilateral	Follow-up duration	$\Delta FEV_1$ (95% CI)	$\Delta RV$ (95% CI)	$\Delta 6MWT$ distance (95% CI)	$\Delta SGRQ$ , total score (95% CI)
<b>EBV</b> Klooster, 2015 (39)	Prospective RCT; Single center	34	hetero	unilateral	6 months	216 mL** (128 to 304) 26.5%* (16.3 to 36.4)		92 m* (64 to 120)	-17.4** (-24.8 to -10.0)
Davey, 2015 (31)	Double-blind, sham-controlled RCT; Single center	25	hetero	unilateral	3 months	0.06 L* (0.02 to 0.38) 8.77%* (2.27 to 35.85)	-0.26 L (-1.07 to -0.16) -6.58% (-18.60 to 2.94)	25 m* (7 to 64)	-4.40 (-16.93 to 6.76)
Herth, 2013 (36)	Non-randomized prospective trial; Multicenter	51 (patients with no CV)	hetero	unilateral	30 days	0.14 ± 0.20 L** 16 ± 22%***	4.49 ± 1.22 L	24 ± 57 m	-10 ± 13
Herth, 2012 (19)	Prospective RCT; Multicenter	44 (Complete fissure), 67 (Incomplete fissure)	hetero	unilateral	12 months	15 ± 29%*		13 ± 35%	0 ± 15
			hetero	unilateral	12 months	0 ± 23%		5 ± 30%	-1 ± 14
Sciurba, 2010 (18)	Prospective RCT; Multicenter	220	hetero	unilateral	6 months	4.3%** (1.4 to 7.2) 34.5 mL** (10.8 to 58.3)		2.5%* (-1.1 to 6.1) 9.3 m* (-0.5 to 19.1)	-2.8* (-4.7 to -1.0)
<b>IBV</b> Wood, 2014 (25)	prospective, adaptive, double-blind RCT; Multicenter	142	hetero	bilateral	6 months	-0.07 ± 0.17 L -2.11 ± 5.49%	0.31 ± 1.00 L 12.57 ± 51.11%	-24.02 ± 69.81 m	2.15 ± 16.36
Nimane, 2012 (24)	Single-blinded sham-controlled RCT; Multicenter	37	hetero	bilateral	3 months	0.99 ± 0.35 L to 0.90 ± 0.34 L	4.65 ± 1.30 L to 4.86 ± 1.35 L	337 ± 106 m to 344 ± 18 m	-4.3 ± 16.2
Eberhardt, 2012 (26)	RCT; Single center	11 (unilateral), 11 (bilateral)	hetero	unilateral (11) bilateral (11)	30 days 30 days	267 ± 154 mL# 13 ± 140 mL	-546 ± 1307 mL -61 ± 990 mL	47.8 ± 55.7 m# -25.0 ± 81.5 m	-12.2 ± 13.4# -0.3 ± 9.8
Sierman, 2010 (23)	Prospective, open enrollment case series; Multicenter	91	hetero	bilateral	12 months	0.87 ± 0.25 L to 0.85 ± 0.33 L	4.74 ± 1.06 L to 4.71 ± 1.27 L	338 ± 95 m to 358 ± 92 m	-9.5 ± 14.4#
<b>LVRC</b> Sciurba, 2016 (67)	Prospective, assessor-blinded RCT; Multicenter	158	both	bilateral	12 months	3.8%** (-6.3 to 16.1)	-0.41 L** (0.57 to -0.25)	10.3 m* (-33.0 to 45.0)	-8.1** (-10.2 to -6.0)
Deslee, 2016 (66)	Prospective, open-label, superiority RCT; Multicenter	50	both	bilateral	6 months	0.06 L** (0.02 to 0.11) 9%* (4 to 14)	-0.52 L* (-0.74 to -0.31) -9%** (-12 to -5)	36% improvement ≥ 54 m* 18 m (-6 to 43)	-11.1** (-15.9 to -6.2)
Klooster, 2014 (63)	Prospective, open-label, cohort trial; Single center	10	homo	bilateral	6 months	0.58 (0.45 to 0.93) to 0.69 (0.56 to 1.02) L#	5.04 (4.14 to 6.57) to 4.44 (3.57 to 5.68) L#	289 (160 to 485) m to 350 (192 to 520) m##	63 (45 to 79) to 48 (25 to 68) #
Deslee, 2014 (62)	Prospective, open-label feasibility study; Multicenter	60	hetero	bilateral	12 months	0.11 ± 0.30 L# 16.0 ± 35.5%#	-0.71 ± 0.81 L# -13.8 ± 12.7%#	51.4 ± 76.1 m#	-11.1 ± 13.3#

\* $p < 0.05$  compared to control, \*\* $p < 0.01$  compared to control, # $p < 0.05$  compared to baseline, ## $p < 0.01$  compared to baseline.  $\Delta$ , change; ABS, airway bypass stents; BioLVRC, biological lung volume reduction; BTVA, bronchoscopic thermal vapor ablation; EBV, endobronchial valve; FEV<sub>1</sub>, forced expiratory volume over 1 second; IBV, intrabronchial valve; LVRC, lung volume reduction coil; RV, residual volume; SGRQ, St. George's Respiratory Questionnaire; 6MWT, 6-min walk test; CV, collateral ventilation.

Table 1. Summary of reported trials on bronchoscopic lung volume reduction (continued)

Device/year (Ref.)	Design	No. of patients treated	Emphysema phenotype: hetero, homo, or both	Procedure unilateral or bilateral	Follow-up duration	$\Delta FEV_1$ (95% CI)	$\Delta RV$ (95% CI)	$\Delta 6MWT$ distance (95% CI)	$\Delta SGRQ$ , total score (95% CI)
Shah, 2013 (64)	Prospective RCT; Multicenter	23	both	bilateral	90 days	14.2%* (6.8 to 21.6)	-0.51 L* (-0.73 to -0.30)	51.2 m** (27.7 to 74.7)	-8.1* (-13.8 to 2.4)
Slebos, 2012 (61)	Prospective, cohort pilot study; Single center	16	hetero	unilateral (12) bilateral (4)	6 months	14.9 ± 17%#	-11.4 ± 9%#	84.4 ± 73.4 m#	-14.9 ± 12.1#
<b>BTVA</b> Herth, 2016 (72)	Prospective, parallel-group, open-label RCT; Multicenter	45	hetero	unilateral	6 months	130.8 mL** (63.6 to 198.0) 11.0 ± 16.2%**	-302.5 mL* (-542.6 to -62.4)	30.5 m (-1.5 to 62.4)	-9.7 ± 14.4**
Snell, 2012 (69)	Two open-label, single-arm studies; Multicenter	44	hetero	unilateral	6 months	140.8 ± 26.3 mL#	-406 ± 112.9 mL#	46.5 ± 15.0 m#	-14.0 ± 2.4#
<b>BioLVR</b> Come, 2015 (78)	Prospective, open-label RCT; Multicenter	59	hetero	bilateral	3 months (n = 34) 6 months (n = 21)	110 mL** (18 to 211)			-11* (-18 to -1)
Kramer, 2012 (76)	Single-arm, prospective study; Multicenter	20	both	bilateral	6 months	335 ± 438 mL# 31.2 ± 36.6%#	-485 ± 981 mL -7.1 ± 19.3%	11.8 ± 57.5 m	-8.0 ± 17.2
Herth, 2011 (74)	Non-controlled, open-label, pilot study; Multicenter	21	hetero	unilateral	6 months	0.105 ± 0.201 L# 10.0 ± 19.8%#		24.6 ± 58.9 m	-7.5 ± 14.4#
Refaely, 2009 (75)	Open-label, non-randomized, phase 2 study; Multicenter	17	homo	bilateral	6 months	13.8 ± 20.26%#		2.6 ± 38.25 m	-12.2 ± 12.38#
<b>ABS</b> Shah, 2011 (81)	Double-blind, sham-controlled RCT; Multicenter	208	homo	bilateral	Day 1 1 month 6 months	3.1 ± 6%** 0.7 ± 4% -0.15 ± 7%	-17.9 ± 38%* -6.8 ± 29% -5.6 ± 32%	302 ± 88 m to 314 ± 95 m 302 ± 88 m to 281 ± 109 m	57 ± 13 to 50 ± 15** 57 ± 13 to 56 ± 16

\* $p < 0.05$  compared to control, \*\* $p < 0.01$  compared to control, # $p < 0.05$  compared to baseline, ## $p < 0.01$  compared to baseline,  $\Delta$ , change; ABS, airway bypass stents; BioLVR, biological lung volume reduction; BTVA, bronchoscopic thermal vapor ablation; EBV, endobronchial valve; FEV<sub>1</sub>, forced expiratory volume over 1 second; IBV, intrabronchial valve; LVR, lung volume reduction coil; RV, residual volume; SGRQ, St. George's Respiratory Questionnaire; 6MWT, 6-min walk test; CV, collateral ventilation.

the target lobe. The balloon is inflated to occlude the airway and the airflow can be measured. If the airflow gradually decreases during measurement, CV is absent (35). A multicenter study reported that the accuracy of CV assessment by Chartis system was 75%. Moreover, 1 month after valve placement, patients with no CV had an improvement of 16% in FEV<sub>1</sub> whereas patients with CV experienced only an increase of 1% in FEV<sub>1</sub> ( $p = 0.0013$ ) (36). However, the existence of CV cannot be determined by the Chartis system in about 10% of patients because of the anatomy of the airway and excessive airway secretions. At this time, a means of high-resolution CT to assess CV is still needed (37).

Only a few studies have compared CT and Chartis at evaluating collateral ventilation. A retrospective study ( $n = 33$ ) indicated that CT was comparable to Chartis in predicting if a TLVR of more than 350 mL ( $p = 0.55$ ) could be achieved in the target lobe; CT had an accuracy of 78.8% and Chartis had an accuracy of 75.8% (34). A retrospective study by Gompelmann *et al.* indicated that the Chartis system had an accuracy of 74% and CT had an accuracy of 77% (38).

Recently, a single-center RCT, known as the STELVIO trial, combined high-resolution CT and the Chartis system to screen patients (39). In this study, 68 patients with no CV according to the Chartis system and an intact interlobular fissure according to high-resolution CT were randomly divided into patients receiving an EBV ( $n = 34$ ) and patients receiving standard treatment ( $n = 34$ ). After 6 months, FEV<sub>1</sub> increased by a mean of 26.5% in patients receiving an EBV and 3.6% in the control group ( $p < 0.001$ ). Improvement in the forced vital capacity (FVC) and results on the 6MWT were also statistically and clinically significant. The combination of fissure analysis using CT and CV measurement with the Chartis system apparently improves the clinical benefit of EBV implantation.

However, the combination of high-resolution CT and the Chartis system in patient selection has its disadvantages. Gompelmann *et al.* reported that a number of patients with no CV and an incomplete interlobular fissure and patients with CV and a complete interlobular fissure can benefit from EBV implantation (38). Although a strategy combining both approaches can provide a clinical benefit, it would inevitably deprive some patients of the opportunity to benefit from treatment.

In a recent retrospective study ( $n = 38$ ), de Oliveira *et al.* proposed new criteria for patient selection (40). The study indicated that TLVR would not exceed 350 mL after EBV implantation in patients with an interlobular fissure that was less than 75% complete ( $n = 8$ ). A TLVR  $\geq 350$  mL was achieved in 19 of 21 patients with interlobular fissure integrity greater than 90% and in 7 of 10 patients of interlobular fissure integrity of 70-90%. The effectiveness of EBV implantation was closely correlated with an interlobular fissure integrity

of more than 75% (the previous standard was more than 90% completeness), and interlobular fissure integrity of more than 75% had an accuracy of 87.2% at predicting a TLVR  $\geq 350$  mL. Therefore, the study's authors contended that EBV implantation should be considered for all patients with interlobular fissure integrity greater than 75% and that EBV implantation should definitely be considered for all patients with interlobular fissure integrity greater than 90%. The authors also indicated that collateral ventilation should be assessed with Chartis in patients with interlobular fissure integrity of 75-90%.

Nevertheless, Schuhmann *et al.* indicated that the response rate was only 65% in patients with fissure integrity greater than 90% (34). Similar results were obtained in studies by Davey *et al.* and Klooster *et al.* (31,39). If the fissure is incomplete ( $< 90\%$ ), the chance of EBV implantation succeeding would be quite small according to Schuhmann *et al.*, and this group of patients would not need to be examined with Chartis (34). Therefore, a strategy combining CT and Chartis can ensure a clinical benefit of EBV implantation and avoid useless treatment of unsuitable patients. The patient selection strategy advocated by de Oliveira *et al.* needs to be studied in more RCTs.

#### 2.2.4. Heterogeneity of emphysema

Heterogeneity of emphysema is another possible predictor of the effectiveness of EBV implantation. Clinical evidence has not led to any definite conclusions regarding this predictor. The VENT study in the US and a retrospective study of 57 patients found greater improvement in patients with more heterogeneous emphysema (18,41). However, the VENT study in Europe found that the extent of heterogeneity had no significant impact on the success of EBV implantation in patients with an intact interlobular fissure and collapse of the target lobe (19). In a study by Herth *et al.*, 14 of 20 patients (70%) with no CV and less heterogeneous emphysema had a TLVR  $\geq 350$  mL after treatment (36). Klooster *et al.* indicated that patients with no CV and an intact interlobular fissure had greater improvement if emphysema was heterogeneous rather than homogeneous, but the difference between the two was not statistically significant (39). Theoretically, more heterogeneous emphysema means non-target lobes on the same side are healthier than the target lobe. If the target lobe collapsed by atelectasis, a healthier lobe on the same side can benefit more from an improvement in respiratory dynamics. Patients with more heterogeneous emphysema should improve more after EBV implantation. Recent studies have not indicated significant differences between high and low heterogeneous emphysema. This may relate to the currently designated values for the threshold of heterogeneity (the average heterogeneity of emphysema in patients who received the minimal clinical benefit in the VENT study). Therefore, whether the heterogeneity

of emphysema can be a predictive index for EBV implantation and its threshold level should be studied further.

### 2.2.5. Other predictors

An EBV can be implanted in the upper or lower lobe of the left or right lung. Retrospective studies of the VENT results indicated that post-procedure lung function improvement did not differ significantly when an upper or lower lobe was treated (42,43). However, recent studies have found that each lobe plays a different role in lung functioning, with the lower lobe of the lung having more of an impact on FEV<sub>1</sub> than the upper lobe (44,45). Therefore, EBV implantation in the lower lobe may have more of a benefit, but this contention needs to be verified. Several studies have indicated that EBV implantation in the left lobe was more likely to achieve a TLVR than implantation in the right lobe (40,42). This may be because the left lobe is less likely to have collateral ventilation than the right lobe (46). In addition, the right lobe has two interlobular fissures while the left lobe has only one; thus, there is a greater likelihood of interlobular collateral ventilation occurring. A study by Davey *et al.* indicated that when the interlobular fissures were intact and there was no collateral ventilation, treatment of the left lobe resulted in better improvement in the FEV<sub>1</sub> than treatment of the right lobe did, but the difference was not significant (31). The sample in the study by Davey *et al.* was too small, and the issue of whether treatment of the left or right lobe affects the effectiveness of EBV implantation needs to be studied further.

In some studies, ventilation/perfusion scintigraphy of the lungs is routinely performed (11-18). The state of lung perfusion is usually consistent with the extent of damage (47), but in a few instances the state of lung perfusion and extent of emphysema may differ because local vascular inflammation has induced vascular remodeling, which can also lead to irregularities in pulmonary perfusion (48,49). Therefore, pulmonary perfusion should be assessed prior to the procedure to comprehensively assess the lungs. Lung perfusion is usually assessed using a combination of CT and single-photon emission computed tomography (SPECT). Every lung perfusion scintigram is craniocaudally divided into three equal parts. The upper part of regional perfusion is similar to the upper lobe of the lung, and the lower part is similar to that of the lower lobe (50). A series of studies found that BLVR would cause a decrease in target lung perfusion and increase ipsilateral non-target lobe and contralateral lung perfusion (51-53). Therefore, assessment of lobe perfusion before treatment may be an index of the success of EBV. A retrospective study of the VENT results found that baseline hypoperfusion of the target lobe improved significant results on the 6MWT after EBV implantation. However, in this study the hypoperfused lobe had more emphysema, so the

extent of emphysema in the target lobe may affect post-procedure results on the 6MWT (54). Thomsen *et al.* indicated that the degree of perfusion of the target lobe and its impact on post-procedure improvement in the 6MWT did not differ significantly, but patients with greater perfusion of the non-target lung on the same side had significant improvement in the 6MWT after treatment (41). Generally speaking, assessment of emphysema (heterogeneity) and pulmonary perfusion together may provide a more comprehensive assessment of the lobes and their state. Treating the affected lobe allows a "better" lobe on the same side to function better and can lead to greater benefits from EBV implantation. This strategy warrants further study with regard to patient selection.

### 2.3. Complications of valve implantation

The main complications of valve implantation are exacerbation of COPD, hemoptysis, pneumothorax, and valve displacement. Pneumothorax is the most common complication. Gompelmann *et al.* found that the more volume reduction in the target lobe, the higher the incidence of pneumothorax (55). Patients with pneumothorax benefit more from receiving EBVs. However, pneumothorax is a serious complication of EBV implantation, patients must be closely monitored for pneumothorax within 72-96 hours of the procedure; patients should be placed on bed rest for 48 hours and be given a cough suppressant since pneumothorax often occurs 4 days after EBV implantation (56). Experts in the treatment of postoperative pneumothorax have reached a consensus: all patients need to be closely observed, and patients with an expanding pneumothorax will need immediate insertion of a chest drain (57). Removal of one or all valves or immediate surgical intervention may be considered for patients with deteriorating clinical symptoms. IBV implantation and EBV implantation involve similar post-procedure complications.

EBVs have been implanted to treat severe emphysema for more than 10 years and are mainly used in patients with unilateral heterogeneous emphysema. EBV treatment is performed in one lobe only once in most patients. A recent retrospective study of patients with emphysema in both lungs received EBV treatment in one lung; if lung function failed to improve or declined again after improving, a second EBV treatment was performed in the opposite lung (58). The study indicated that patients receiving a 2-steps EBV treatment in both lungs could also benefit from the second procedure; there were no significant differences in post-procedure complications for patients receiving EBV treatment in one or both lungs although the latter had a longer hospital stay. Further RCTs need to be conducted to evaluate the effectiveness of this sequential EBV treatment in both lungs.

Ongoing RCTs of EBV implantation aim to optimize patient screening (LIBERATE study, NCT01796392), evaluate long-term outcomes (LIVE study, NCT01580215), to treat patients with mild to moderate COPD (REMODEL study, NCT01969734), and to treat patients with homogeneous emphysema (IMPACT study, NCT02025205). Ongoing RCTs of IBV implantation include complete occlusion of target lobe in one lung with implanted IBVs (EMPROVE study, NCT01812447; SVS study, NCT01989182) and an open-label study of IBV implantation in patients with no CV (NCT01902732).

### 3. Non-blocking BLVR

#### 3.1. LVRC

LVRC (PneumRx/BTG, Camberley, UK) involves the use of nickel-titanium alloy coils 10-20 cm long. A delivery system is used to place the straightened coils in an affected lung. The coils regain their shape and compress lung tissue affected by emphysema; as the tissue is compressed, its volume is reduced, directing air to healthier portions of the lung, thus achieving a reduction in lung volume (59). LVRC can be used for treatment of bilateral or unilateral emphysema. For patients with bilateral emphysema, treatment usually involves 2 steps: treatment of the lung on one side and then treatment of the lung on the other side 1-4 months later. Whether patients have collateral ventilation does not need to be considered in LVRC, and LVRC can target the most severely damaged pulmonary segment for treatment instead of the entire lobe, thus leaving as much healthy lung tissue intact as possible. LVRC has obvious advantages over EBV implantation. However, the disadvantage of LVRC is that it is partially irreversible since removal of coils is difficult and is certainly not feasible in all cases.

Small early trials indicated the safety and effectiveness of LVRC (60,61). A prospective European multicenter single-arm study involving 60 patients with bilateral heterogeneous emphysema found that FEV<sub>1</sub>, results on the 6MWT, and scores on the SGRQ improved significantly at the 1-year follow-up (62). A small-scale study by Klooster *et al.* suggested that LVRC might be equally effective in treating both homogeneous and heterogeneous emphysema (63). In the RESET study, 47 patients with homogeneous or heterogeneous emphysema were randomly assigned to either an LVRC treatment group or the control group (64). The treatment group consisted of 23 patients who underwent bilateral LVRC implantation. Three months after the procedure, lung function, exercise capacity, and quality of life improved significantly in comparison to the control group. There was no significant difference in the benefit received by patients with homogeneous or heterogeneous emphysema in that study. One year

after the procedure, patients were still found to benefit from the treatment (65). In a multicenter RCT, known as the REVOLENS trial, 100 patients with bilateral emphysema were assigned to receive LVRC treatment or standard care. After 6 months, significantly more patients in the treatment group ( $n = 50$ ) had an improvement of 54 m in the 6MWT in comparison to the control group ( $n = 50$ ) (36% of patients,  $n = 18$  vs. 17% of patients,  $n = 9$ ), although the absolute between-group difference in results on the 6MWT was only modest (21 m) (66). The study sample was carefully selected to include patients with a residual volume greater than 220% of the predicted volume, which represents a higher degree of expiratory air trapping and contrasts with the 150% predicted volume specified in inclusion criteria for most BLVR trials. A recent RCT ( $n = 315$ ), known as the RENEW trial, required a residual volume of greater than 175% of the predicted volume. In comparison to standard care, implantation of LVRCs only resulted in a modest improvement in exercise capacity and slight improvement in lung function, with a higher likelihood of post-procedure complications. However, a subgroup analysis indicated that patients with homogeneous or heterogeneous emphysema and a residual volume of greater than 225% of the predicted volume had a significant improvement in lung function and quality of life because of LVRC implantation (67). Usually there are few choices for treatment of patients with homogeneous emphysema besides conventional treatment (more than 75% cannot undergo LVRS or some other BLVR), so LVRC offers a treatment option. Therefore, patients with a high degree of air trapping may be the main beneficiaries of LVRC treatment. Whether LVRC treatment is able to increase the long-term survival of patients needs to be verified by further studies.

The main complications of LVRC treatment include exacerbation of COPD, hemoptysis, transient chest pain, pneumonia, and pneumothorax; most complications occur within a few weeks after LVRC implantation, but mild hemoptysis may persist for a few months after the procedure (60).

#### 3.2. BTVA

BTVA (Uptake Medical Corporation, Seattle, Wash., USA) delivers water heated by an endobronchial catheter to the affected lobe to induce an inflammatory response, leading to irreversible pulmonary parenchymal fibrosis, scar formation, and distal atelectasis, thus achieving a reduction in lung volume (68). Thus far, BTVA has only been used to treat patients with heterogeneous emphysema primarily in the upper lung regions. BTVA can treat the most affected segment of one lobe, regardless of collateral ventilation. However, this technique is irreversible.

A single-arm multicenter study of 44 patients with



upper lobe emphysema indicated that patients receiving unilateral BTVA had an improved FEV<sub>1</sub> of 140.8 mL ( $p < 0.001$ ) after 6 months, and 58% of patients had 12% improvement in their FEV<sub>1</sub> (69). However, the inflammatory reaction causes most patients to develop complications such as a fever, cough, sputum, and hemoptysis in the 4 weeks after the procedure; the inflammatory response gradually subsides after 12 weeks but it prolongs hospitalization. Nevertheless, the inflammatory reaction seems to be necessary for the success of BTVA. Patients who develop an inflammatory reaction have a better clinical outcome than patients without respiratory adverse events after BTVA (70). Henne *et al.* wondered whether BTVA at a lower dose would reduce the incidence of complications and provide benefits similar to those of BTVA at a higher dose (71). Recently, the multicenter STEP-UP study compared 46 patients who received low-dose BTVA with 24 patients who received standard care (72). The study used 8.5 calories of vapor energy per gram of lung tissue to treat affected segments, in contrast to 10 calories per gram used in previous trials. In order to reduce post-procedure complications, the treatment was performed in two steps. The first procedure treated the most severely damaged pulmonary segment of a lobe, and the second procedure treated the remaining segments of the same lobe 3-4 months later. After 6 months, the trial group had significant changes in its FEV<sub>1</sub> (improvement of 14.7% in the BTVA group vs. the control group,  $p < 0.0001$ ) and its scores on the SGRQ (reduction of 9.7 points in the BTVA group,  $p = 0.0021$ ). Furthermore, the incidence of adverse events decreased significantly in comparison to that in previous BTVA trials. STEP-UP study is the only RCT involving BTVA. Further studies are needed to verify the long-term survival benefit of BTVA.

### 3.3. BioLVR

BioLVR is another irreversible BLVR technique using an emphysematous lung sealant system (Aeris Therapeutics, Woburn, Mass., USA). BioLVR involves injecting synthetic polymers to block the airways of affected regions in order to promote bronchial remodeling, scarring, and atelectasis, resulting in a reduction in target lung hyperinflation (73).

Previous studies indicated that BioLVR achieved a reduction in lung volume. Six months after BioLVR, patients had significant improvement in their FEV<sub>1</sub> and scores on the SGRQ, and patients with advanced heterogeneous emphysema generally tolerated the procedure (74). Another study indicated that BioLVR improved lung function and quality of life for patients with homogeneous emphysema (75). A study by Kramer *et al.* indicated that BioLVR is effective in treating both heterogeneous and homogeneous emphysema, and benefits in patients with heterogeneous or homogeneous

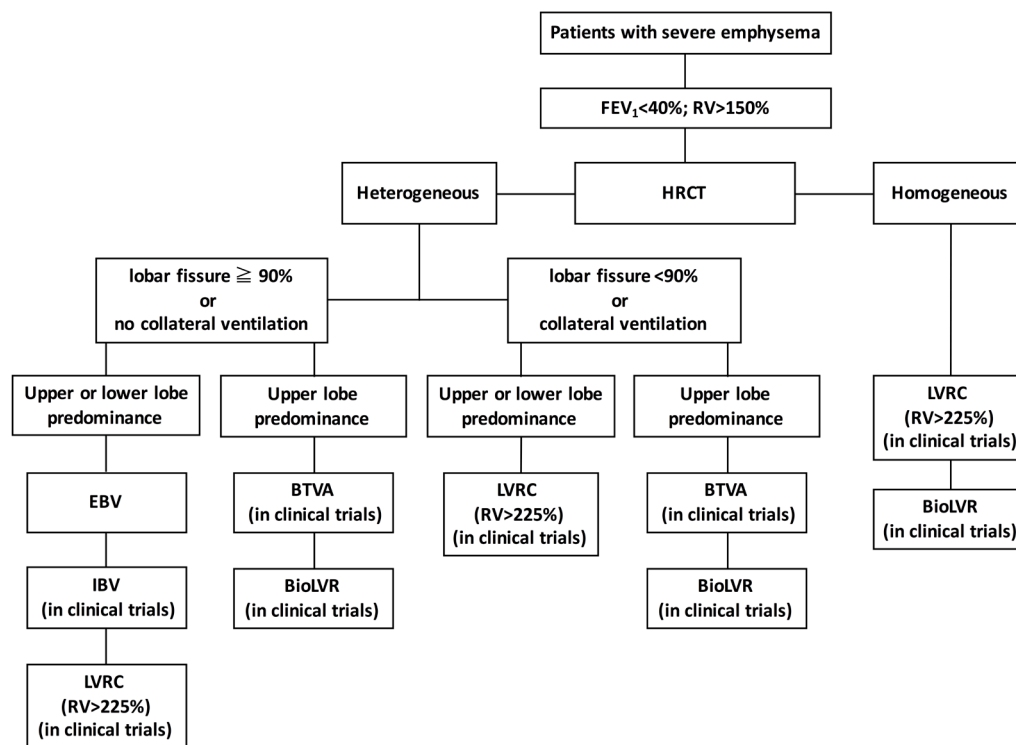
emphysema did not differ significantly 2 years after treatment (76,77). Magnussen *et al.* found that whether interlobular fissures were complete had no obvious effect on the effectiveness of BioLVR (73). In a recent RCT, known as the ASPIRE study, Come *et al.* compared patients undergoing BioLVR and a control group receiving standard care, and they found that 34 patients who underwent BioLVR had a significantly improved quality of life (FEV<sub>1</sub>: 11.4 % vs. -2.1%,  $p = 0.0037$ ; SGRQ: -11 vs. -4,  $p = 0.026$ ) (78). Six months after treatment, these improvements were still evident, and more than 50% of patients who underwent BioLVR had a clinically significant improvement (improvement in FEV<sub>1</sub>  $\geq 12$  % or improvement in scores on the SGRQ  $\geq 4$ ); however, 44% of treated patients had respiratory complications requiring hospitalization at the 90-day follow-up and two deaths were reported. The major complications of BioLVR are a fever, cough, chest pain, acute exacerbation of COPD, pneumonia, and hemoptysis. BioLVR needs to be evaluated further in clinical trials.

### 3.4. ABS

ABS is mainly used in patients with severe homogeneous emphysema. ABS provides a bypass so that gas trapped in an affected region of the lung can be released, thus reducing lung volume. Studies have indicated that ABS can improve pulmonary function and the symptom of dyspnea, but this improvement did not differ significantly between the treatment group and the control group (79,80). In 2011, a multicenter, double-blind, sham-controlled RCT, known as the EASE trial, randomly divided 315 patients with severe homogeneous emphysema into an ABS group ( $n = 208$ ) and a sham surgery group ( $n = 107$ ); follow-up assessments revealed no statistically significant differences in FEV<sub>1</sub>, results on the 6MWT, or scores on the SGRQ for either group after 6 months (81). The trial did not achieve the expected primary endpoint (at the 6-month follow-up, FVC increased by at least 12% and mMRC fell by 1 point from the baseline). However, the trial indicated that ABS in the short term had certain curative effects. However, these effects gradually disappeared over time. This may be because ABS failed to open up a route for gas to escape because the ABS shifted, the respiratory tract was obstructed by secretions, or granulation tissue formed. Optimizing the design of the ABS and sustaining its effectiveness over the long term need to be explored further. ABS needs to bridge a vast divide to be ready for clinical use.

## 4. Conclusion

The high mortality and morbidity rate of LVRS has spurred the development of BLVR. Previous trials and follow-up data have indicated that BLVR can be used to



**Figure 1. Recommended algorithm for bronchoscopic lung volume reduction in patients with severe emphysema in accordance with the distribution of emphysema and the presence or absence of collateral ventilation.** BioLVR, biological lung volume reduction; BTVA, bronchoscopic thermal vapor ablation; EBV, endobronchial valve; FEV<sub>1</sub>, forced expiratory volume over 1 second; IBV, intrabronchial valve; LVRC, lung volume reduction coil; RV, residual volume.

treat patients with severe emphysema. However, BLVR has yet to yield satisfactory results in terms of the improvement in pulmonary function, exercise capacity, and quality of life and the incidence of complications. The long-term benefit of BLVR needs to be studied further. More work is needed to define patient selection criteria for each individual technique. According to the research, the current options for BLVR to treat patients with emphysema are as shown in Figure 1. This algorithm is similar with those proposed by previous studies, but is modified based on the latest studies and clinical evidence (82,83). Future research will focus on devising new criteria for patient selection and improving patient benefit while expanding the pool of eligible patients. As imaging and clinical indicators are studied further, clinicians of the future may choose a different BLVR technique based on more accurate patient characteristics, achieving "precision medicine" for patients with emphysema.

In summary, BLVR is a minimally invasive treatment for severe emphysema, providing treatment options for patients who are unable to undergo LVRS or lung transplantation. This technique may be of great value in improving lung function, exercise capacity, and quality of life, and it has the potential to replace conventional surgery for patients with severe emphysema. Optimal patient selection and the proper selection of the BLVR technique in accordance with

patient characteristics are crucial to the success of BLVR. More multicenter, prospective RCTs need to be conducted in the future.

#### Acknowledgements

This work was supported by the Capital Clinical Innovative Application Research Project of Beijing Municipal Science and Technology Commission (No. Z141107002514009).

#### References

1. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbri LM, Martinez FJ, Nishimura M, Stockley RA, Sin DD, Rodriguez-Roisin R. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med.* 2013; 187:347-365.
2. Murray CJ, Lopez AD. Measuring the global burden of disease. *N Engl J Med.* 2013; 369:448-457.
3. World Health Organization. Burden of COPD. <http://www.who.int/respiratory/copd/burden/en/> (accessed July 28, 2016).
4. Kemp SV, Polkey MI, Shah PL. The epidemiology, etiology, clinical features, and natural history of emphysema. *Thorac Surg Clin.* 2009; 19:149-158.
5. Brantigan OC, Mueller E. Surgical treatment of pulmonary emphysema. *Am Surg.* 1957; 23:789-804.

6. Washko GR, Fan VS, Ramsey SD, Mohsenifar Z, Martinez F, Make BJ, Scierba FC, Criner GJ, Minai O, Decamp MM, Reilly JJ, National Emphysema Treatment Trial Research Group. The effect of lung volume reduction surgery on chronic obstructive pulmonary disease exacerbations. *Am J Respir Crit Care Med.* 2008; 177:164-169.
7. Fishman A, Martinez F, Naunheim K, Piantadosi S, Wise R, Ries A, Weinmann G, Wood DE, 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.
8. Hosenpud JD, Bennett LE, Keck BM, Edwards EB, Novick RJ. Effect of diagnosis on survival benefit of lung transplantation for end-stage lung disease. *Lancet.* 1998; 351:24-27.
9. Stavem K, Bjortuft O, Borgan O, Geiran O, Boe J. Lung transplantation in patients with chronic obstructive pulmonary disease in a national cohort is without obvious survival benefit. *J Heart Lung Transplant.* 2006; 25:75-84.
10. Ingenito EP, Reilly JJ, Mentzer SJ, Swanson SJ, Vin R, Keuhn H, Berger RL, Hoffman A. Bronchoscopic volume reduction: A safe and effective alternative to surgical therapy for emphysema. *Am J Respir Crit Care Med.* 2001; 164:295-301.
11. 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.
12. Snell GI, Holsworth L, Borrill ZL, Thomson KR, Kalfv V, Smith JA, Williams TJ. The potential for bronchoscopic lung volume reduction using bronchial prostheses. *Chest.* 2003; 124:1073-1080.
13. Yim AP, Hwong TM, Lee TW, Li WW, Lam S, Yeung TK, Hui DS, Ko FW, Sihoe AD, Thung KH, Arifi AA. Early results of endoscopic lung volume reduction for emphysema. *J Thorac Cardiovasc Surg.* 2004; 127:1564-1573.
14. Venuta F, de 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 heterogenous emphysema. *Ann Thorac Surg.* 2005; 79:411-416; discussion 416-417.
15. de Oliveira HG, Macedo-Neto AV, John AB, Jungblut S, Prolla JC, Menna-Barreto SS, Fortis EA. Transbronchoscopic pulmonary emphysema treatment: 1-month to 24-month endoscopic follow-up. *Chest.* 2006; 130:190-199.
16. Hopkinson NS, Toma TP, Hansell DM, Goldstraw P, Moxham J, Geddes DM, Polkey MI. Effect of bronchoscopic lung volume reduction on dynamic hyperinflation and exercise in emphysema. *Am J Respir Crit Care Med.* 2005; 171:453-460.
17. Wan IY, Toma TP, Geddes DM, Snell G, Williams T, Venuta F, Yim AP. Bronchoscopic lung volume reduction for end-stage emphysema: Report on the first 98 patients. *Chest.* 2006; 129:518-526.
18. Scierba FC, Ernst A, Herth FJ, Strange C, Criner GJ, Marquette CH, Kovitz KL, Chiacchierini RP, Goldin J, McLennan G, Group VSR. A randomized study of endobronchial valves for advanced emphysema. *N Engl J Med.* 2010; 363:1233-1244.
19. Herth FJ, Noppen M, Valipour A, Leroy S, Vergnon JM, Ficker JH, Egan JJ, Gasparini S, Agusti C, Holmes-Higgin D, Ernst A, International VENT Study Group. Efficacy predictors of lung volume reduction with Zephyr valves in a European cohort. *Eur Respir J.* 2012; 39:1334-1342.
20. Valipour A, Herth FJ, Burghuber OC, Criner G, Vergnon JM, Goldin J, Scierba F, Ernst A, VENT Study Group. Target lobe volume reduction and COPD outcome measures after endobronchial valve therapy. *Eur Respir J.* 2014; 43:387-396.
21. 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.
22. Venuta F, Anile M, Diso D, Carillo C, De Giacomo T, D'Andrilli A, Fraioli F, Rendina EA, Coloni GF. Long-term follow-up after bronchoscopic lung volume reduction in patients with emphysema. *Eur Respir J.* 2012; 39:1084-1089.
23. Sterman DH, Mehta AC, Wood DE, *et al.* A multicenter pilot study of a bronchial valve for the treatment of severe emphysema. *Respiration.* 2010; 79:222-233.
24. Ninane V, Geltner C, Bezzi M, *et al.* Multicentre European study for the treatment of advanced emphysema with bronchial valves. *Eur Respir J.* 2012; 39:1319-1325.
25. Wood DE, Nader DA, Springmeyer SC, *et al.* The IBV Valve trial: A multicenter, randomized, double-blind trial of endobronchial therapy for severe emphysema. *J Bronchology Interv Pulmonol.* 2014; 21:288-297.
26. Eberhardt R, Gompelmann D, Schuhmann M, Heussel CP, Herth FJ. Complete unilateral vs partial bilateral endoscopic lung volume reduction in patients with bilateral lung emphysema. *Chest.* 2012; 142:900-908.
27. Kohn HN. Zur Histologie des indurierenden fibrinösen Pneumonie. *Münch Med Wochenschr* 1893; 40:42-45.
28. Lambert MW. Accessory bronchiole-alveolar communications. *J Pathol Bacteriol.* 1955; 70:311-314.
29. Martin HB. Respiratory bronchioles as the pathway for collateral ventilation. *J Appl Physiol.* 1966; 2:1443-1447.
30. Gompelmann D, Eberhardt R, Herth FJ. Collateral ventilation. *Respiration.* 2013; 85:515-520.
31. Davey C, Zoumot Z, Jordan S, McNulty WH, Carr DH, Hind MD, Hansell DM, Rubens MB, Banya W, Polkey MI, Shah PL, Hopkinson NS. Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HiFi study): A randomised controlled trial. *Lancet.* 2015; 386:1066-1073.
32. Koenigkam-Santos M, Puderbach M, Gompelmann D, Eberhardt R, Herth F, Kauzcor HU, Heussel CP. Incomplete fissures in severe emphysematous patients evaluated with MDCT: Incidence and interobserver agreement among radiologists and pneumologists. *Eur J Radiol.* 2012; 81:4161-4166.
33. van Rikxoort EM, Goldin JG, Galperin-Aizenberg M, Abtin F, Kim HJ, Lu P, van Ginneken B, Shaw G, Brown MS. A method for the automatic quantification of the completeness of pulmonary fissures: Evaluation in a database of subjects with severe emphysema. *Eur Radiol.* 2012; 22:302-309.
34. Schuhmann M, Raffy P, Yin Y, Gompelmann D, Oguz I, Eberhardt R, Hornberg D, Heussel CP, Wood S, Herth FJ. Computed tomography predictors of response to endobronchial valve lung reduction treatment: Comparison with Chartis. *Am J Respir Crit Care Med.* 2015; 191:767-774.
35. 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; 80:419-425.
36. Herth FJ, Eberhardt R, Gompelmann D, Ficker JH, Wagner M, Ek L, Schmidt B, Slebos DJ. Radiological and clinical outcomes of using Chartis to plan endobronchial valve treatment. *Eur Respir J*. 2013; 41:302-308.
  37. Shah PL, Herth FJ. Dynamic expiratory airway collapse and evaluation of collateral ventilation with Chartis. *Thorax*. 2014; 69:290-291.
  38. Gompelmann D, Eberhardt R, Slebos DJ, Brown MS, Abtin F, Kim HJ, Holmes-Higgin D, Radhakrishnan S, Herth FJ, Goldin J. Diagnostic performance comparison of the Chartis System and high-resolution computerized tomography fissure analysis for planning endoscopic lung volume reduction. *Respirology*. 2014; 19:524-530.
  39. Klooster K, ten Hacken NH, Hartman JE, Kerstjens HA, van Rikxoort EM, Slebos DJ. Endobronchial valves for emphysema without interlobar collateral ventilation. *N Engl J Med*. 2015; 373:2325-2335.
  40. de Oliveira HG, de Oliveira SM, Rambo RR, de Macedo Neto AV. Fissure integrity and volume reduction in emphysema: A retrospective study. *Respiration*. 2016; 91:471-479.
  41. Thomsen C, Theilig D, Herzog D, Poellinger A, Doellinger F, Schreiter N, Schreiter V, Schurmann D, Temmesfeld-Wollbrueck B, Hippenstiel S, Suttorp N, Hubner RH. Lung perfusion and emphysema distribution affect the outcome of endobronchial valve therapy. *Int J Chron Obstruct Pulmon Dis*. 2016; 11:1245-1259.
  42. Liberator C, Shenoy K, Marchetti N, Criner G. The role of lobe selection on FEV<sub>1</sub> response in endobronchial valve therapy. *COPD*. 2016; 13:477-482.
  43. Eberhardt R, Herth FJ, Radhakrishnan S, Gompelmann D. Comparing clinical outcomes in upper versus lower lobe endobronchial valve treatment in severe emphysema. *Respiration*. 2015; 90:314-320.
  44. Matsuo K, Iwano S, Okada T, Koike W, Naganawa S. 3D-CT lung volumetry using multidetector row computed tomography: Pulmonary function of each anatomic lobe. *J Thorac Imaging*. 2012; 27:164-170.
  45. Kitano M, Iwano S, Hashimoto N, Matsuo K, Hasegawa Y, Naganawa S. Lobar analysis of collapsibility indices to assess functional lung volumes in COPD patients. *Int J Chron Obstruct Pulmon Dis*. 2014; 9:1347-1356.
  46. Herzog D, Hippenstiel S, Schürmann D, *et al*. Prevalence of interlobar collateral ventilation in COPD patients. *Eur Respir J*. 2014; 44 (Suppl 58):3714.
  47. Hueper K, Vogel-Claussen J, Parikh MA, *et al*. Pulmonary microvascular blood flow in mild chronic obstructive pulmonary disease and emphysema. The MESA COPD Study. *Am J Respir Crit Care Med*. 2015; 192:570-580.
  48. Harkness LM, Kanabar V, Sharma HS, Westergren-Thorsson G, Larsson-Callertfelt AK. Pulmonary vascular changes in asthma and COPD. *Pulm Pharmacol Ther*. 2014; 29:144-155.
  49. Santos S, Peinado VI, Ramírez J, Melgosa T, Roca J, Rodríguez-Roisin R, Barberà JA. Characterization of pulmonary vascular remodelling in smokers and patients with mild COPD. *Eur Respir J*. 2002; 19:632-638.
  50. Chandra D, Lipson DA, Hoffman EA, Hansen-Flaschen J, Sciruba FC, Decamp MM, Reilly JJ, Washko GR, National Emphysema Treatment Trial Research Group. Perfusion scintigraphy and patient selection for lung volume reduction surgery. *Am J Respir Crit Care Med*. 2010; 182:937-946.
  51. Pizarro C, Ahmadzadehfar H, Essler M, Fimmers R, Nickenig G, Skowasch D. Volumetric and scintigraphic changes following endoscopic lung volume reduction. *Eur Respir J*. 2015; 45:262-265.
  52. Pizarro C, Ahmadzadehfar H, Essler M, Tuleta I, Fimmers R, Nickenig G, Skowasch D. Effect of endobronchial valve therapy on pulmonary perfusion and ventilation distribution. *PLoS One*. 2015; 10:e0118976.
  53. Brown MS, Kim HJ, Abtin FG, Strange C, Galperin-Aizenberg M, Pais R, Da Costa IG, Ordoookhani A, Chong D, Ni C, McNitt-Gray MF, Tashkin DP, Goldin JG. Emphysema lung lobe volume reduction: Effects on the ipsilateral and contralateral lobes. *Eur Radiol*. 2012; 22:1547-1555.
  54. Argula RG, Strange C, Ramakrishnan V, Goldin J. Baseline regional perfusion impacts exercise response to endobronchial valve therapy in advanced pulmonary emphysema. *Chest*. 2013; 144:1578-1586.
  55. Gompelmann D, Herth FJ, Slebos DJ, Valipour A, Ernst A, Criner GJ, Eberhardt R. Pneumothorax following endobronchial valve therapy and its impact on clinical outcomes in severe emphysema. *Respiration*. 2014; 87:485-491.
  56. Herzog D, Poellinger A, Doellinger F, Schuermann D, Temmesfeld-Wollbrueck B, Froeling V, Schreiter NF, Neumann K, Hippenstiel S, Suttorp N, Hubner RH. Modifying post-operative medical care after EBV implant may reduce pneumothorax incidence. *PLoS One*. 2015; 10:e0128097.
  57. Valipour A, Slebos DJ, de Oliveira HG, Eberhardt R, Freitag L, Criner GJ, Herth FJ. Expert statement: Pneumothorax associated with endoscopic valve therapy for emphysema--potential mechanisms, treatment algorithm, and case examples. *Respiration*. 2014; 87:513-521.
  58. Fiorelli A, D'Andrilli A, Anile M, Diso D, Poggi C, Polverino M, Failla G, Venuta F, Rendina EA, Santini M. Sequential bilateral bronchoscopic lung volume reduction with one-way valves for heterogeneous emphysema. *Ann Thorac Surg*. 2016; 102:287-294.
  59. Klooster K, Ten Hacken NH, Slebos DJ. The lung volume reduction coil for the treatment of emphysema: A new therapy in development. *Expert Rev Med Devices*. 2014; 11:481-489.
  60. Herth FJ, Eberhard R, Gompelmann D, Slebos DJ, Ernst A. Bronchoscopic lung volume reduction with a dedicated coil: A clinical pilot study. *Ther Adv Respir Dis*. 2010; 4:225-231.
  61. Slebos DJ, Klooster K, Ernst A, Herth FJ, Kerstjens HA. Bronchoscopic lung volume reduction coil treatment of patients with severe heterogeneous emphysema. *Chest*. 2012; 142:574-582.
  62. Deslee G, Klooster K, Hetzel M, Stanzel F, Kessler R, Marquette CH, Witt C, Blaas S, Gesierich W, Herth FJ, Hetzel J, van Rikxoort EM, Slebos DJ. Lung volume reduction coil treatment for patients with severe emphysema: A European multicentre trial. *Thorax*. 2014; 69:980-986.
  63. Klooster K, Ten Hacken NH, Franz I, Kerstjens HA, van Rikxoort EM, Slebos DJ. Lung volume reduction coil treatment in chronic obstructive pulmonary disease patients with homogeneous emphysema: A prospective feasibility trial. *Respiration*. 2014; 88:116-125.
  64. Shah PL, Zoumot Z, Singh S, Bicknell SR, Ross ET,

- Quiring J, Hopkinson NS, Kemp SV. Endobronchial coils for the treatment of severe emphysema with hyperinflation (RESET): A randomised controlled trial. *Lancet Respir Med.* 2013; 1:233-240.
65. Zoumot Z, Kemp SV, Singh S, Bicknell SR, McNulty WH, Hopkinson NS, Ross ET, Shah PL. Endobronchial coils for severe emphysema are effective up to 12 months following treatment: Medium term and cross-over results from a randomised controlled trial. *PLoS One.* 2015; 10:e0122656.
66. Deslee G, Mal H, Dutau H, *et al.* Lung volume reduction coil treatment vs. usual care in patients with severe emphysema: The REVOLENS Randomized Clinical Trial. *JAMA.* 2016; 315:175-184.
67. Scieurba FC, Criner GJ, Strange C, *et al.* Effect of endobronchial coils vs. usual care on exercise tolerance in patients with severe emphysema: The RENEW Randomized Clinical Trial. *JAMA.* 2016; 315:2178-2189.
68. Gompelmann D, Heussel CP, Eberhardt R, Snell G, Hopkins P, Baker K, Witt C, Valipour A, Wagner M, Stanzel F, Egan J, Ernst A, Kesten S, Herth FJ. Efficacy of bronchoscopic thermal vapor ablation and lobar fissure completeness in patients with heterogeneous emphysema. *Respiration.* 2012; 83:400-406.
69. Snell G, Herth FJ, Hopkins P, Baker KM, Witt C, Gotfried MH, Valipour A, Wagner M, Stanzel F, Egan JJ, Kesten S, Ernst A. Bronchoscopic thermal vapour ablation therapy in the management of heterogeneous emphysema. *Eur Respir J.* 2012; 39:1326-1333.
70. Gompelmann D, Eberhardt R, Ernst A, Hopkins P, Egan J, Stanzel F, Valipour A, Wagner M, Witt C, Baker KM, Gotfried MH, Kesten S, Snell G, Herth FJ. The localized inflammatory response to bronchoscopic thermal vapor ablation. *Respiration.* 2013; 86:324-331.
71. Henne E, Kesten S, Herth FJ. Evaluation of energy in heated water vapor for the application of lung volume reduction in patients with severe emphysema. *Respiration.* 2013; 85:493-499.
72. Herth FJ, Valipour A, Shah PL, *et al.* Segmental volume reduction using thermal vapour ablation in patients with severe emphysema: 6-month results of the multicentre, parallel-group, open-label, randomised controlled STEP-UP trial. *Lancet Respir Med.* 2016; 4:185-193.
73. Magnussen H, Kramer MR, Kirsten AM, Marquette C, Valipour A, Stanzel F, Bonnet R, Behr J, Fruchter O, Refaely Y, Eberhardt R, Herth FJ. Effect of fissure integrity on lung volume reduction using a polymer sealant in advanced emphysema. *Thorax.* 2012; 67:302-308.
74. Herth FJ, Gompelmann D, Stanzel F, Bonnet R, Behr J, Schmidt B, Magnussen H, Ernst A, Eberhardt R. Treatment of advanced emphysema with emphysematous lung sealant (AeriSeal®). *Respiration.* 2011; 82:36-45.
75. Refaely Y, Dransfield M, Kramer MR, Gotfried M, Leeds W, McLennan G, Tewari S, Krasna M, Criner GJ. Biologic lung volume reduction therapy for advanced homogeneous emphysema. *Eur Respir J.* 2010; 36:20-27.
76. Kramer MR, Refaely Y, Maimon N, Rosengarten D, Fruchter O. Bilateral endoscopic sealant lung volume reduction therapy for advanced emphysema. *Chest.* 2012; 142:1111-1117.
77. Kramer MR, Refaely Y, Maimon N, Rosengarten D, Fruchter O. Two-year follow-up in patients treated with emphysematous lung sealant for advanced emphysema. *Chest.* 2013; 144:1677-1680.
78. Come CE, Kramer MR, Dransfield MT, *et al.* A randomised trial of lung sealant versus medical therapy for advanced emphysema. *Eur Respir J.* 2015; 46:651-662.
79. Choong CK, Cardoso PF, Sybrecht GW, Cooper JD. Airway bypass treatment of severe homogeneous emphysema: Taking advantage of collateral ventilation. *Thorac Surg Clin.* 2009; 19:239-245.
80. Cardoso PF, Snell GI, Hopkins P, Sybrecht GW, Stamatis G, Ng AW, Eng P. Clinical application of airway bypass with paclitaxel-eluting stents: Early results. *J Thorac Cardiovasc Surg.* 2007; 134:974-981.
81. Shah PL, Slebos DJ, Cardoso PFG, Cetti E, Voelker K, Levine B, Russell ME, Goldin J, Brown M, Cooper JD, Sybrecht GW. Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial): Randomised, sham-controlled, multicentre trial. *Lancet.* 2011; 378:997-1005.
82. Shah PL, Herth FJ. Current status of bronchoscopic lung volume reduction with endobronchial valves. *Thorax.* 2014; 69:280-286.
83. Eberhardt R, Gompelmann D, Herth FJ, Schuhmann M. Endoscopic bronchial valve treatment: Patient selection and special considerations. *Int J Chron Obstruct Pulmon Dis.* 2015; 10:2147-2157.

(Received June 20, 2016; Revised August 7, 2016; Accepted August 9, 2016)