Review Article

Bronchoscopic lung volume reduction: who, what, where, when?

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Abstract: Chronic obstructive pulmonary disease (COPD) is a significant source of morbidity and mortality globally. The number of afflicted individuals is expected to increase for the foreseeable future. Endoscopic lung volume reduction (ELVR) modalities have recently been introduced as an alternative to more invasive lung volume reduction surgery (LVRS) for severe emphysema. Endoscopic tools include one-way valves, coils, thermal vapor ablation, and sealant. These devices are broadly classified as "block" and "non-block" strategies. They differ in terms of the requirement for fissure integrity, whether they are applied at the lobar or segmental level, their reversibility, and whether they are applicable for homogenous and/or heterogenous disease. Endobronchial valves (EBVs) are now being used outside of clinical trials and are supported by multiple guidelines. These valves reduce hyperinflation by promoting lobar atelectasis in the absence of collateral ventilation (CV), which can now be quantified using specialized software and intra-procedural analysis. Patient selection criteria continue to be refined as more data become available. Pneumothorax is the most common adverse event but does not appear to affect outcomes if it is appropriately managed. Multiple ongoing trials are investigating the impact of different devices and strategies in order to improve long-term outcomes. Other modalities for ELVR are under development. Herein, we review the impact of COPD on population health and discuss the role of endobronchial procedural interventions in its management.

Keywords: Bronchoscopic lung volume reduction; endobronchial valves (EBVs); endobronchial coils; emphysema; lung volume reduction surgery (LVRS)

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Introduction

Chronic obstructive pulmonary disease (COPD) affects over 10% of the world's population (1). It is the third leading cause of mortality worldwide, and the number of affected individuals continues to increase due to continued exposure to risk factors and an aging population (1,2). In 2012, more than 3 million people died from COPD, accounting for 6% of all deaths worldwide (2). Hospitalizations are predicted to increase by >150% over the next 15 years in developed countries, while the number of people with COPD over age 75 years of age is predicted to increase by 220% (3). It is a progressive condition, most commonly caused by cigarette smoking. Other etiologies include genetic conditions (alpha-1 antitrypsin deficiency) and environmental (biomass fuel, air pollution, etc.) and occupational exposures in approximately 10% of cases (4). Symptoms include cough and dyspnea, resulting in reduced exercise capacity.

Treatment is stage dependent and has historically included bronchodilators, pulmonary rehabilitation, and smoking cessation (5). Adherence to therapy has been demonstrated to improve surrogate outcome measures,

Table 1 Characteristics of various ELVR modalities

ELVR technique	Block *vs.* non-block	Fissure integrity required	Lobar *vs.* segmental therapy	FDA approved	Reversible	Type of emphysema	Mechanism of action
Zephyr® valve	Blocking	Yes	Lobar	Yes	Yes	Homogenous or heterogenous	Reduces air trapping
Spiration® valve	Blocking	Yes	Lobar	Yes	Yes	Heterogenous	Reduces air trapping
Coils	Non-blocking	No	Lobar	No	Partially	Homogenous or heterogenous	Improves elastic recoil
Thermal vapor ablation	Non-blocking	No	Segmental	No	No	Heterogenous, only upper lobe	Local inflammatory reaction
Sealant	Blocking	No	Sub-segmental	No	No	Heterogenous, only upper lobe	Reduces air trapping

ELVR, endoscopic lung volume reduction.

including number of exacerbations, spirometry, and quality of life (QoL) (6). Bronchodilators include long-acting muscarinic antagonists, long-acting beta agonists, and inhaled corticosteroids. Refractory cases may also utilize chronic oral corticosteroids, chronic suppressive antibiotics, phosphodiesterase inhibitors, and supplemental oxygen (7). For patients with emphysema, options beyond medical management have historically been limited to very select patients and have involved surgical treatment with either lung volume reduction surgery (LVRS) or lung transplantation (8). The National Emphysema Treatment Trial (NETT) demonstrated improved pulmonary function, exercise capacity, and QoL with LVRS in patients with upper lobe predominant emphysema and poor baseline exercise capacity (9,10). High morbidity, mortality, and costs have hindered its widespread adoption (11-13).

Since the introduction of LVRS, various endoscopic lung volume reduction (ELVR) modalities have been developed (*Table 1*). ELVR options commercially available globally include valves, coils, vapor, and sealant (14). Of these, only valves are approved for use in the United States (US). Broadly, these techniques can be classified as "block" [endobronchial valve (EBV), sealant] and "non-block" (coils, vapor) (15). The same groupings also apply to their reversibility, except for sealant. Valves include the Zephyr® Endobronchial Valve (Pulmonx, Redwood City, CA, USA) and the Spiration® Valve System (SVS) (Olympus, Tokyo, Japan). EBVs have now been incorporated into guidelines, including those from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the National Institute for Health and Care Excellence (NICE) (16,17). They are also approved by the US Food and Drug Administration (FDA) since 2018 (18,19). Attention will be focused on EBVs for the remainder of the discussion since they are the only ELVR modality currently in widespread use outside of clinical trials.

Physiologic rationale

A subset of patients with COPD develop emphysematous destruction of parenchymal tissue due to chronic inflammation. In turn, this causes permanent enlargement of the terminal bronchioles, which leads to impaired gas exchange, dynamic hyperinflation, loss of elastic recoil, air trapping, and increased residual volume (RV) (20). Hyperinflation impairs normal respiratory muscle mechanics and decreases chest wall compliance (21). As work of breathing increases, exercise tolerance decreases, creating a vicious cycle. While traditional pharmacologic therapy for COPD decreases respiratory symptoms and improves exercise capacity, it does not reverse the underlying pathophysiology or the trajectory of deteriorating respiratory function.

LVRS is based on the principle of resecting the most damaged lobe in patients with heterogeneous upper lobe predominant emphysema, thereby reducing hyperinflation. This reduction decreases pressure on the chest wall and respiratory muscles, including the diaphragm, allowing them to assume a more natural conformation and hence function more effectively.

EBVs have been designed to achieve the same reduction in hyperinflation as LVRS but with less morbidity and mortality. They are intended to produce complete occlusion of the segmental or subsegmental airways in a lobe, which

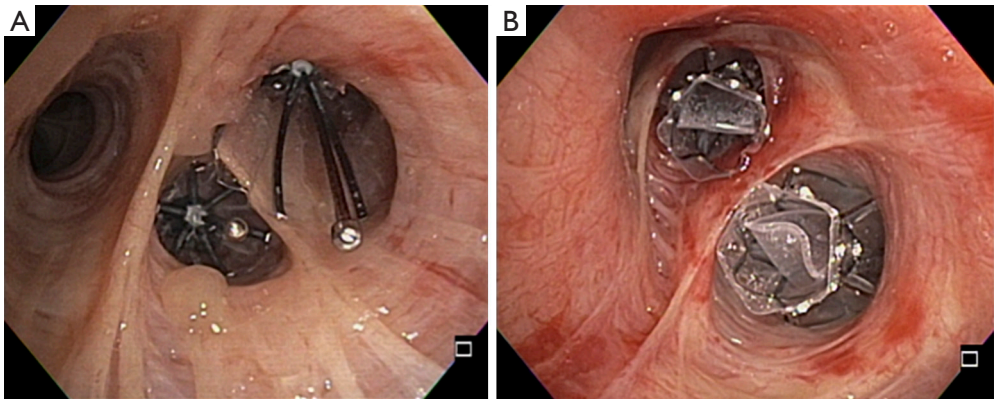

Figure 1 Two types of US FDA approved EBVs. (A) Spiration® valve characterized by its umbrella-like shape and anchors; (B) Zephyr® valve demonstrating its classic duckbill shape. EBV, endobronchial valve.

Table 2 Comparison of the two types of EBVs

Valve characteristics	Zephyr®	Spiration®
Frame	Nitinol	Nitinol
Membrane	Silicone	Polyurethane
Sizes	2 (each is available in 2 lengths)	4
Shape	Duckbill	Umbrella
Mechanism of position maintenance	Radial expansile force	Anchors

EBV, endobronchial valve.

should lead to lobar atelectasis if there is no collateral ventilation (CV). At least a 350 mL reduction in volume is necessary for patients to appreciate a clinical benefit (22). Identification of CV is discussed in more detail in the section on patient selection.

Endobronchial valves

The Spiration® and Zephyr® valves differ in their structure and composition, as seen in *Figure 1*. While both are built using a nitinol (combination of nickel and titanium) framework, the Spiration® valve has an umbrella-like shape and utilizes a polyurethane covering (*Table 2*). The Zephyr® valve is duckbill shaped and employs a silicone covering. Although structurally unique, both valves are designed to achieve the same outcome—lobar atelectasis via complete one-way occlusion of the airway. In order to achieve this result, CV must be absent. Both valves allow unidirectional flow in the proximal direction during expiration, so that the treated lobe is vented (23). This allows atelectasis to develop and produce the desired volume-reducing effect.

Different techniques are required to measure airway diameter and ensure appropriate fit. The SVS uses a balloon catheter that must be carefully calibrated preoperatively, while the Zephyr® valve relies on two sets of small wings attached to the distal aspect of the deployment catheter. These wings approximate the diameter of the two valve sizes. After measuring the airway diameter, they are deployed through a flexible bronchoscope using a catheter inserted via the working channel. After positioning the catheter appropriately, the sheath is retracted, and the EBV springs open and into position. Because precise positioning is required, these procedures are most often performed under general anesthesia in an endoscopy suite or operating room. Radial force against the airway wall limits migration with the Zephyr® valve, while anchors help maintain position of the Spiration® valve.

Patient selection

Candidates for EBVs must meet a number of criteria.

Table 3 Recommended and optional diagnostic testing

Recommended tests	Optional tests
Pulmonary function testing (spirometry with bronchodilator, lung volumes measured with body plethysmography, and diffusion capacity)	RHC
TTE	NM SPECT CT
ABG on room air for ≥10 minutes	
6MWT	
HRCT chest	

RHC, right heart catheterization; TTE, transthoracic echocardiogram; NM SPECT CT, nuclear medicine single photon emission tomography computed tomography; ABG, arterial blood gas; 6MWT, 6-minute walk test; HRCT, high-resolution computed tomography.

First and foremost, they must have emphysema with hyperinflation and be highly symptomatic despite receiving optimal pharmacologic management, including bronchodilators, inhaled corticosteroids, and systemic therapy if necessary. Smoking cessation for at least 4 months is mandatory. They should have completed or be actively enrolled in a formal pulmonary rehabilitation program or comparable structured physical therapy program. Nutritional status should be optimized with the help of a dietician. Chronic hypoxic respiratory failure necessitating supplemental oxygen at home is not an absolute contraindication. Contraindications include inability to tolerate a bronchoscopic procedure, active pulmonary infection, active smoking, allergy to the device material, and large bullae occupying greater than one-third of the lung (18,19). In the clinical trials, patients with a mean pulmonary artery systolic pressure (PASP) >45 mmHg and/or with a $PaCO_2$ >50 mmHg were excluded (24,25).

The medical evaluation consists of complete pulmonary function testing (spirometry with a bronchodilator, diffusion capacity, and lung volumes obtained via body plethysmography), a volumetric high-resolution computed tomography (HRCT) scan, a 6-minute walk test (6MWT), a transthoracic echocardiogram (TTE), and an arterial blood gas (ABG) on room air (*Table 3*). Acceptable values for this testing based on LIBERATE and EMPROVE trial criteria are delineated in *Table 4* (26). A right heart catheterization (RHC) may be required to rule out pulmonary hypertension (PH) when the TTE suggests a right ventricular systolic pressure (RVSP) >50 mmHg.

Computer analysis of the HRCT quantifies the degree of emphysematous destruction by lobe and fissure completeness, which is thought to correspond with interlobar CV. Utilization of this quantitative imaging software is recommended by an expert panel (26). Reports for the two approved EBVs have slight differences. The SeleCT® Report used for the SVS provides a calculated heterogeneity score. The StratX® Report used for the Zephyr valve provides emphysema destruction scores for threshold values of both –910 and –950 Hounsfield units (HU). It also provides a combined measurement for the right upper and middle lobes, in addition to the right upper lobe individually.

The more complete the fissure, the less likely there is to be CV. The ideal HRCT protocol involves a non-contrast scan on a multi-detector platform with thin (0.6–1.25 mm) slices with some overlap and smooth kernel reconstructions. The exact protocol depends on the manufacturer of the HRCT equipment. Incidental findings, including bronchiectasis, pulmonary nodules, and interstitial fibrosis should be addressed prior to proceeding with ELVR. A threshold value of >40–50% destruction (percentage of voxels <–910 HU) is utilized when identifying an acceptable target lobe (24,25). Heterogenous emphysema is typically defined as an absolute difference ≥10–15% in the destruction scores between the target lobe and the ipsilateral lobe(s) (24,25,27).

When there are two or more acceptable target lobes based on computer analysis of the HRCT, a nuclear medicine single photon emission tomography computed tomography (NM SPECT CT) scan may be performed to quantify the degree of ventilation and perfusion by lobe of the lungs, in order to identify the optimal target lobe. Among the potential target lobes, the one with the least perfusion should be selected preferentially in order to minimize the amount of ventilation/perfusion (V/Q) mismatching that occurs after lobar occlusion with EBVs (28).

With StratX® analysis software (used for Zephyr® valves),

Table 4 General inclusion criteria for EBV candidates according to the LIBERATE and EMPROVE trials

Methods	LIBERATE trial	EMPROVE trial
FEV_1 post-bronchodilator	15–45% predicted	≤45%
RV	≥175% predicted	≥150% predicted
TLC	>100% predicted	
DLCO	≥20% predicted	NR
6MWT	100–450 m	≥140 m
PH	RVSP <45 mmHg	"not severe by clinical evaluation"
EF	≥45%	NR
PaO_2	>45 mmHg on room air	
$PaCO_2$	<50 mmHg on room air	
BMI	<35	>15
Smoking cessation	≥4 months	
CV determination	Fissure integrity score >85% on quantitative CT analysis preoperatively & Chartis® flow sensor intraoperatively	Fissure integrity ≥90% on quantitative CT analysis
Heterogeneity	≥15%	≥10%
Emphysema score	≥50% using –910 HU	≥40% using –920 HU

EBV, endobronchial valve; FEV_1, forced expiratory volume in 1 s; RV, residual volume; TLC, total lung capacity; DLCO, diffusing capacity of the lung for carbon monoxide; 6MWT, 6-minute walk test; PH, pulmonary hypertension; RVSP, right ventricular systolic pressure; EF, ejection fraction; NR, not reported; CV, collateral ventilation; CT, computed tomography; HU, Hounsfield units.

fissure completeness scores (FCSs) of ≥95% and ≤80% are defined as complete and incomplete, respectively. Scores in the 80–95% range are defined as partially complete. In this subgroup of patients, Chartis® (Pulmonx Inc., Redwood City, CA, USA) assessment is recommended to assist with identifying the presence of CV and has an overall accuracy of 83.3% (26,29). The Chartis® system is a balloon catheter that measures pressure, flow, and resistance after balloon occlusion of a lobar bronchus. Lack of CV is confirmed when the air flow decreases to zero after occlusion of an airway. Chartis® assessment is optional above 95% fissure completeness and unnecessary <80%, since these latter patients are not candidates for EBVs. Chartis® assessment can be safely and accurately performed under either moderate sedation or general anesthesia (22). Early studies suggested that together, computer analysis of the HRCT and the Chartis® assessment have a pooled sensitivity of 75% for detecting CV (30). Recent data have shown that for the left and right major fissures, a FCS >95% has a sensitivity of 91.1% and 73.7%, respectively (31). Thus, Chartis® assessment is recommended on the right regardless of quantitative CT fissure analysis.

There are no data using the Chartis® system with Spiration® valves. CT scan analysis using different software was performed in the EMPROVE trial, where a ≥90% fissure integrity threshold was utilized (24). This software differs in that no combined assessment of the right upper lobe and right middle lobe is provided. Heterogeneity is also reported. For reference, the EMPROVE thresholds are listed on the report, and values meeting those criteria are highlighted.

Management of complications

EBVs have rapidly gained popularity because of the low morbidity and mortality rate associated with this therapy. Complications, however, still occur and must be addressed. A recent meta-analysis identified the following risk ratios (RRs) (32):

- Pneumothorax RR: 9.65 (3.04–30.6);
- Mild hemoptysis RR: 6.42 (1.21–34.01);
- Hospitalization for a COPD exacerbation RR: 2.01 (1.19–3.40).

These adverse events were not associated with

Table 5 Comparison of trial results between the LIBERATE and EMPROVE studies

Outcomes	LIBERATE	EMPROVE
Target lobe volume reduction, mL	–1,142	–974
ΔFEV_1, mL	106	101
ΔRV, mL	–490	–361
Δ6MWD, m	39	15
SGRQ, points	–7.1	–8.5

FEV_1, forced expiratory volume in 1 s; RV, residual volume; 6MWD, 6-minute walk distance; SGRQ, St. George's Respiratory Questionnaire.

a significant risk of death [RR: 1.56 (0.47–5.18)] or pneumonia [RR: 2.17 (0.86–5.49)].

The most common adverse event is pneumothorax, which is more likely with complete lobar atelectasis, especially when it occurs rapidly. Pneumothorax occurs because of compensatory over-expansion of the ipsilateral untreated lobe(s) (33). In both the EMPROVE and LIBERATE trials, the majority of pneumothoraces occurred within the first 72 hours, so close observation in the hospital is recommended for at least 3 days postoperatively (24-26). Tube thoracostomy drainage alone is usually sufficient. If drainage is not performed in an expeditious manner, tension pneumothorax may develop and could be fatal. A management algorithm has been developed by Valipour *et al*. for refractory cases (34). If a persistent air leak (PAL) continues beyond 7 days, then removal of one EBV is recommended. If the PAL still continues for 48 hours, then remove the remaining valves. If the PAL still fails to resolve, then consider pleurodesis or surgical intervention. There is no role for prophylactic tube thoracostomy intraoperatively.

There is no role for preoperative steroids. Some authors also recommend steroids and prophylactic antibiotic therapy for 1 week after ELVR to reduce inflammation and the risk of a COPD exacerbation or pneumonia (23). Limited data are available to support this practice.

Evidence

A number of randomized controlled trials (RCTs) have been conducted with both types of EBVs in order to demonstrate safety and efficacy. Key findings from the trials that led to US FDA approval are summarized below and presented in *Table 5*.

Zephyr® valve

The multicenter RCT of Zephyr® Endobronchial Valve Treatment in Heterogeneous Emphysema (LIBERATE) trial randomized 190 subjects in a 2:1 ratio to treatment with EBV and standard of care (SoC) at 24 sites (25). At 12 months, forced expiratory volume in 1 s (FEV_1) improved ≥15% in 47.7% and 16.8% in the EBV group and SoC group, respectively (P<0.001). The absolute improvement in the EBV group versus the SoC group was statistically and clinically significant in the following categories: FEV_1 106 mL (P<0.001), 6-minute walk distance (6MWD) +39.31 m (P=0.002), St. George's Respiratory Questionnaire (SGRQ) –7.05 points (P=0.004), hyperinflation (i.e., RV) –522 mL (P<0.001), modified Medical Research Council (mMRC) –0.8 points (P<0.001), and the body mass index, airflow obstruction, dyspnea, and exercise capacity (BODE) score –1.2 points. The study authors concluded that the Zephyr® EBV provided clinically meaningful improvement in lung function, exercise capacity, and QoL at the 12-month mark. The most common complication was pneumothorax, which occurred in 26.6% of the EBV group subjects within the first 45 days.

Spiration® valve

The SVS was studied in the EMPROVE trial, which was a multicenter RCT in patients with heterogeneous emphysema (24). In this study, 172 subjects were randomized in a 2:1 ratio to either the SVS or SoC. At 12 months, the valve group had improvements in FEV_1 (99 mL), SGRQ (–9.5 points), and 6MWD (+6.9 m). COPD exacerbations and pneumothorax were the most common adverse events. Within the first 6 months, the valve group experienced a 12.4% rate of serious pneumothorax, defined as those requiring tube thoracostomy drainage. As with the LIBERATE trial, the majority of these pneumothoraces occurred within the first 72 hours.

Survival

Survival after ELVR has been the subject of several recent studies (35-37). In a post hoc analysis of the STELVIO (Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation) trial, Klooster *et al*. suggested the potential for improved survival with EBV therapy based on improvements observed at 6 months in the BODE index, 6MWD, and inspiratory capacity to total lung capacity

(IC/TLC) ratio, all of which have previously been shown to predict risk of death in patients with severe COPD (35,38).

In the most recent study, Gompelmann *et al.* demonstrated that lobar atelectasis following EBV insertion was associated with a significant 5-year survival advantage compared to those patients that did not develop atelectasis (65.3 *vs.* 43.9% 5-year survival rate; P=0.009) (37). Importantly, pneumothorax did not have a significant effect on survival (P=0.52). Pneumothorax is not necessarily indicative of procedural success; lobar atelectasis usually occurs without associated pneumothorax.

Ongoing studies

A number of studies are also ongoing. Several (Elevate study, Reaction study, Next Step study, and the STAGE trial) pertain to the non-EBV ELVR modalities that were not the focus of this review. The NCT03010449 trial is a single-arm study examining the combination of bronchoscopic autologous blood instillation in combination with EBVs. The NTR5007 trial is a single-arm study assessing the proactive treatment of CV in CV-positive patients before treatment with EBVs. The NCT03034421 trial is studying pneumothorax risk by randomizing patients to SoC or 48-hour bedrest after EBV insertion. The NCT03205826 study is examining the impact of Chartis® assessment performed under moderate sedation versus general anesthesia. The SOLVE trial is assessing the impact of pulmonary rehabilitation done either before or after EBV treatment. The NCT03518177 trial is designed to examine if there is any difference in effectiveness between home-based and supervised pulmonary rehabilitation in EBV candidates. Finally, the CELEB trial (ISRCTN19684749) is comparing LVRS and ELVR via EBVs head-to-head.

Guidelines

National and international guidelines (GOLD, NICE, etc.) have been developed to guide management (4,16). The GOLD guidelines provide the following information on interventional therapy in stable COPD:

- LVRS—improves survival in patients with severe emphysema that is upper-lobe predominant and who have a low exercise capacity (Evidence A);
- Bullectomy—associated with decreased dyspnea, improved pulmonary function, and exercise tolerance (Evidence C);
- Transplantation—improves QoL and functional capacity in select patients (Evidence C);
- ELVR—reduces end-expiratory lung volume and improves exercise tolerance, health status, and lung function (Evidence A for EBV, Evidence B for coils, & Evidence B for vapor ablation).

Conclusions

ELVR in general, and EBVs in particular, have become a viable option for patients with refractory respiratory symptoms despite optimal treatment of their emphysema. Numerous RCTs have demonstrated safety and clinical efficacy in the appropriate patient population. It may result in improved lung function, exercise tolerance, and QoL, without the morbidity and mortality of LVRS. Patient selection and optimal post-EBV insertion management remain areas of active research. Long-term outcomes beyond 12 months will need to be examined as data emerge.

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Footnote

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