Bronchoscopic Lung Volume Reduction

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KEYWORDS

• COPD • Emphysema • Bronchoscopic lung volume reduction • Endobronchial valves • Coils

KEY POINTS

- Bronchoscopic lung volume reduction (BLVR) has been shown to be an effective and safe nonsurgical alternative for a select group of emphysema patients.
- Careful evaluation and selection of candidates at centers with expertise in BLVR and interventional pulmonology are key factors in obtaining better clinical outcomes.
- Currently, coils and unidirectional endobronchial valves (EBVs) are the devices more widely used for BLVR. The choice of each specific device depends on the emphysema characteristics (homogeneous vs heterogeneous), presence or absence of lobar collateral ventilation (CV), and underlying comorbidities.
- These interventions are designed to add to the overall care of advanced emphysema patients and contribute to a comprehensive and multidisciplinary approach to the management of chronic obstructive pulmonary disease.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) usually presents as either chronic bronchitis or emphysema and it affects quality of life, leading to disability and early death.[1] It is one of the main causes of death in the world.[2]

Emphysema is defined as the progressive and irreversible destruction of alveolar sacs leading to a loss of lung recoil, early airway collapse, and loss of alveolar gas exchange surface area.[3] Airway collapse leads to air trapping and its presence has correlated with an increase in mortality.[4] In addition to static air trapping, patients develop dynamic hyperinflation, which leads to exercise intolerance and physical deconditioning.[5]

Standard treatment of COPD involves smoking cessation, therapies, such as long-acting bronchodilators and anticholinergic agents, oxygen therapy, and pulmonary rehabilitation programs.[6] Unfortunately, many patients continue to decline despite such comprehensive approach and experience an increase in exacerbations and worsening in exercise tolerance. Such irreversible decline prompted the need to identify additional therapeutic interventions for this specific high-risk patient population.[7]

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EARLY LUNG VOLUME REDUCTION TECHNIQUES

The National Emphysema Treatment Trial (NETT),[7] a multicenter, prospective, randomized study, evaluated the efficacy of surgical lung volume reduction (LVR) compared with standard emphysema management. The study revealed an improvement in exercise tolerance and survival benefit in patients who had upper lobe-predominant emphysema (heterogeneous emphysema pattern) and a poor baseline exercise capacity. It also, however, showed a higher mortality rate and postoperative complications in the treatment group.

Given the potential clinical benefit of volume reduction shown by NETT but with a high surgical risk, less-invasive interventions have been studied and developed, especially in the field of bronchoscopic LVR (BLVR). Most of the BLVR studies have adopted inclusion and exclusion criteria as well as outcome measures from NETT design.[7]

CLINICAL OUTCOMES

Since the NETT design and its clinical outcomes, several variables have been identified to evaluate a functional response to BLVR. They typically include forced expiratory volume in 1 second (FEV_1), residual volume (RV), and total lung capacity (TLC) as determined by plethysmography; 6-minute walk test (6MWT) distance; modified Medical Research Council (mMRC) scale; and quality-of-life scale as determined by St George's Respiratory Questionnaire (SGRQ).

Previous studies have suggested a minimal clinically important difference (MCID) for the main parameters.

- FEV_1 (improvement by 0.10 L or $\geq$12%)[8]
- 6MWT (improvement by $\geq$26 m)[9]
- SGRQ (improvement by $\geq$4 points)[10]
- RV (improvement of at least 0.31–0.43 L, or decrease in RV% from baseline of 6.1%–8.6%)[11]

EARLY LUNG VOLUME REDUCTION ENDOSCOPIC APPROACHES

Early attempts to achieve volume reduction included Watanabe's Spigots (Novatech, La Ciotat, France), which are silicone devices used to occlude the lung segments that are more severely affected by emphysema. The results only showed a minimal benefit for BLVR and its current use focuses on management of bronchopleural fistula and persistent air leak.[12,13]

A technique of Airway Bypass (Broncus Technologies, San Jose, California) was designed to create extra-anatomic passages between the hyperinflated lung parenchyma and larger airways with the goal of decreasing air trapping.[14] This was evaluated in the EASE (Exale Airway Stents for Emphysema) trial,[15] which only showed short-term benefit and the technique is no longer used.

CURRENT TECHNIQUES

The more promising and clinically beneficial techniques in current use include unidirectional intrabronchial valves (IBVs), EBVs, and endobronchial coils. Both types of devices (valves and coils) are discussed in detail later.

Table 1 compares relevant clinical and functional characteristics of both main BLVR techniques.

UNIDIRECTIONAL VALVES

The main purpose of unidirectional valves is to occlude the targeted lobe and through a unidirectional valve-like effect cause atelectasis and volume reduction in the treated area.[16] There are 2 types of valves available and both are made of silicone and nitinol, a metal alloy of nickel and titanium. Both valves are introduced through the working channel of a greater than or equal to 2.8-mm therapeutic bronchoscope. The intervention is usually unilateral. Its main advantage compared with other endobronchial devices is that the valves can be removed if there is no clear clinical benefit, or in case of complications. An average of 3 to 4 valves is usually placed per

Table 1
Practical comparison between coils and endobronchial valves

	Coils	Endobronchial Valves
Treatment	Bilateral	Unilateral
Sedation	General anesthesia	Conscious sedation
Procedure reversibility	No	Yes
Average number of devices per lobe	10–14 coils	3–4 valves
Airway bleeding risk	Mild to moderate	Low
Pneumothorax risk	Yes	Yes
Safe in patients with PH	No	Unclear

lobe. Patients with absence of interlobar CV are more likely to have a positive clinical response to EBV treatment.[17] CV corresponds to the ventilation of alveolar structures through passages or channels that bypass the normal airways.[16,18]

There are 2 different types of commercially available valves. The Spiration IBV (Olympus Respiratory America, Redmond, Washington) (**Fig. 1**) is an umbrella-shaped device that is placed in the different segments of the treated lobe. It is available in 5-mm, 6-mm, 7-mm, and 9-mm sizes. The data suggest a limited clinical benefit[19,20] and its current use is mostly limited to the management of persistent air leak.[21] The Zephyr EBVs (Pulmonx, Redwood City, California) (**Fig. 2**) is a type of valve that has a duckbill shape and is available in 2 different diameter sizes: 4 mm (which includes short and normal length) and 5.5 mm.

The clinical benefits of this treatment were initially reported in the 2010 VENT study (Endobronchial Valve for Emphysema Palliation Trial), a multicenter randomized controlled study comparing EBVs with standard of care treatment of COPD. It revealed an increase in mean between-group difference in FEV_1 of 6.8% ($P = .005$).[22] An enhanced response was seen in the presence of greater radiographic evidence of emphysema heterogeneity and fissure completeness (an intact or complete fissure correlates with absence of alveolar ventilation). The treatment group also showed a higher frequency of respiratory complications, including COPD exacerbations requiring hospitalization, and hemoptysis.

This trial was followed by the BeLieVer HIFi study (Bronchoscopic Lung Volume Reduction with endobronchial valves for patients with Heterogeneous emphysema and Intact interlobar Fissures).[23] It compared BLVR with EBVs and bronchoscopy with sham valve placement, in patients with heterogenous emphysema and intact interlobar fissures by CT in the target lobe. At a 3-month follow-up, FEV_1 increased by a mean 24.8% (95% CI, 8.0–41.5) from baseline in the BLVR group versus 3.9% (95% CI, 0.7–7.1). There was a significant change in 6MWT distance but no significant improvement in SGRQ.

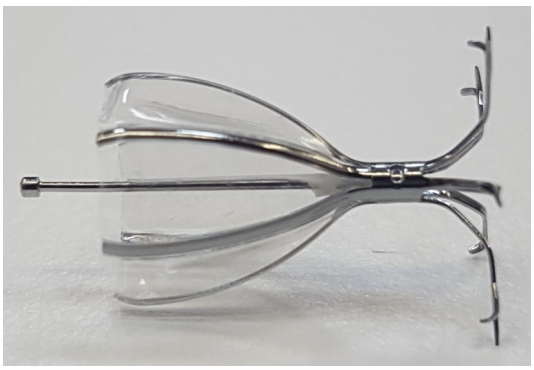

Fig. 1. Spiration IBV. (*Courtesy of* Olympus Respiratory America, Redmond, WA.)

We conducted a randomized, controlled study, called STELVIO, to examine the effectiveness of endobronchial-valve treatment in patients with severe emphysema in whom the absence of collateral ventilation had been proved.[17] The study demonstrated functional improvement in patients with emphysema without CV, when compared with a control group. Absence of CV was objectively determined by the use of Chartis (Pulmonx)

More recently, the IMPACT study[24] compared the use of Zephyr EBVs in patients with homogeneous emphysema—as determined by CT imaging—and absence of CV with a control group. Patients treated with EBVs displayed an improvement in functional parameters and quality of life measures at 3 months.

A recent meta-analysis by Kumar and colleagues[25] on the use of EBVs (Spiration and Zephyr valves) for BLVR revealed a pooled mean difference (PMD) benefit for FEV_1 of 0.146 L (95% CI, 0.111–0.181; $P<.001$), 6MWT of 45.225 m (95% CI, 26.954–63.495; $P<.001$), and SGRQ of −8.825 points (95% CI, 14.824 to −2.825; $P = .004$). PMDs were all statistically significant and were higher than the suggested MCID for each variable.

Based on the available literature discussed previously, it seems that unilateral EBV treatment is a safe intervention. It is also effective in improving functional capacity and quality of life in patients with emphysema -heterogeneous and homogeneous—as long as there is documentation of lobar exclusion (ie, absence of CV).

COILS

Coils (RePneu, BTG, Mountain View, California) (**Fig. 3**) are shape-memory nitinol devices that are implanted bronchoscopically using fluoroscopic guidance. They are straightened for deployment and gather up loose parenchyma as they revert to their original double-loop shape within the airway. The average number of coils placed per treated lobe is 10 to 14. The main objective of the coils is to restore the elastic recoil helping avoid the early airway collapse.[26,27]

Commercially available sizes include 100 mm, 125 mm, and 150 mm, which correspond to the total length of the device. The treatment is bilateral and it is done with a sequential approach and an interval of 4 weeks to 6 weeks in between treatments. It is considered a permanent treatment.

Early clinical trials included a multicenter feasibility study on 60 patients by Deslee and

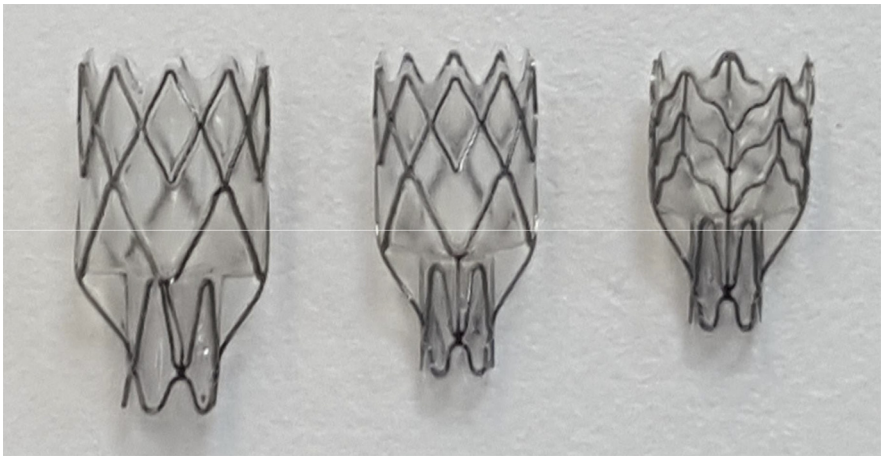

Fig. 2. Zephyr EBVs. Different sizes available, from left to right: 5.5 mm, 4 mm, and 4 mm low profile. (*Courtesy of* Pulmonx, Redwood City, CA.)

colleagues[28] that showed sustained clinical and statistical significant benefits at 1 year. Most of the patients (55 of 60) were treated bilaterally.

The RESET study[29] was the first nonblinded multicenter randomized trial (coils vs standard medical care) on 47 patients with severe emphysema and hyperinflation. It showed a between-group difference of 8.36 points in SGRQ ($P = .04$) in favor of the coil group at 90 days after final treatment. There was also a significant improvement in 6MWT and pulmonary function numbers.

A 2015 meta-analysis by Slebos and colleagues[30] evaluated 4 independent European studies that included 140 patients with similar clinical and functional profiles, to assess efficacy and safety outcomes. It revealed positive clinical outcomes at 6 months and 12 months of follow-up. There was no difference between homogeneous and heterogeneous emphysema. A higher baseline RV was a predictor of successful outcome. Complications included COPD exacerbations and pneumonias. The pneumothorax rate was 6.8%.

Fig. 3. Nitinol coil. (*Courtesy of* RePneu, BTG, Mountain View, CA. ©2018. PneumRx, Inc.)

The REVOLENS[31] study (Réduction Volumique Endobronchique par Spirales) was published in early 2016 and it compared the clinical benefits of coils with standard treatment at 6 months and 12 months in 100 patients with COPD. It was a randomized controlled study conducted in 10 French centers. The primary outcome chosen was an increase of 54 m,[32] which was observed in 18 patients (36%) in the coil group and 9 patients (18%) in the control group ($P = .03$) at 6 months ($P = .03$). Mean between-group differences at 6 months and 12 months in the coil and usual care groups were significant for FEV_1 and SGRQ. A total of 4 deaths occurred in the coil group and 3 in the usual care group by 12 months.

The RENEW study[33] was published in mid-2016 and included 315 patients from 26 centers (21 North American and 5 European). Its primary goal was an increase in 6MWT of 25 m (minimally important clinical difference [MICD]) at 12 months. It found a significant but modest clinical improvement in 6MWT (between-group difference 14.6 m; $P = .02$). An increment of at least 25 m was seen in 40% of coil patients compared with 26.9% in the standard-treatment group ($P = .01$). Major complications, such as pneumonia requiring hospitalization and other potentially life-threatening or fatal events, occurred in 34.8% of coil participants versus 19.1% of usual care ($P = .002$). There was no difference in deaths. Participants with RV greater than or equal to 225% and heterogeneous emphysema distribution had better treatment responses.

The meta-analysis by Kumar and colleagues[25] on the use of coils revealed PMD for FEV_1 of 0.080 L (95% CI, 0.057–0.104; $P<.001$), 6MWT of 45.320 m

(95% CI, 28.040–62.600; $P<.001$), and SGRQ of −10.570 points (95% CI,13.299 to −7.841; $P<.001$). All 3 variables showed statistically significant PMDs but the PMD for FEV_1 was smaller than the proposed MCID (FEV_1 >0.10 L or >12%).

ADDITIONAL TREATMENT TARGETS

Biologic Lung Volume Reduction

The initial techniques used direct application of a sealant/remodeling system to the affected segmental airways with a goal of collapsing areas of the emphysematous lung.[34]

This led to the development of an emphysematous lung sealant (ELS), a synthetic polymeric foam known as AeriSeal (Aeris Therapeutics, Woburn, Massachusetts). An initial open-label noncontrolled study suggested clinical benefits at 24 weeks.[35] This was followed by the ASPIRE trial (Study of the AeriSeal System for HyPerInflation Reduction in Emphysema), a randomized multicenter trial of ELS versus medical treatment.[36] The study was terminated early for business reasons. Analysis of the available data suggested significant statistical and clinical improvement in the ELS group at 3 months and 6 months. Adverse events requiring hospitalization were significantly higher, however, in the treatment group, which might limit its utility.

Thermal Airway Ablation

This technique administers steam vapor directly to the segmental airways most affected by emphysema, using a reusable vapor generator and a disposable bronchoscopic catheter that delivers heated water vapor. The goal is to cause a local inflammatory reaction that causes occlusion and atelectasis of each chosen segment.[37]

A recent multicenter randomized controlled study using thermal vapor ablation, the STEP-UP trial (Sequential Staged Treatment of Emphysema with Upper Lobe Predominance), showed a significant improvement in FEV_1 and SGRQ at 6 months.[38] COPD exacerbation was the most common serious adverse event. Evidence of significant long-term benefit with this technique is still lacking though.

OUTCOMES COMPARISON OF DIFFERENT TECHNIQUES

Given the diversity of the techniques currently available and in development, comparison of outcomes can be confusing. **Table 2** provides a summary from a 2017 Cochrane Review that shed light on this topic comparing the different clinical and functional outcomes.[39] These outcomes can be interpreted in the context of MCIDs, described previously.

TREATMENT PROTOCOLS AND FOLLOW-UP

Centers with expertise in the procedures, discussed previously, typically admit the patients the day prior to the procedure. The following items describe a typical sequence for most cases undergoing BLVR at the authors' center.

- Patient is admitted the day prior to the intervention.
- Standard COPD treatment is continued.
- Broad-spectrum antibiotics, oral steroids, and around-the-clock short-acting β-agonists and anticholinergic agents are initiated on admission.
- Antiplatelet and anticoagulant agents are routinely held, similar to other bronchoscopy procedures. Need for anticoagulation, except for low-dose acetylsalicylic acid (ASA), is a

Table 2
Summary of clinical outcomes of different available techniques included

	Aeriseal	Airway Bypass	Coils	Zephyr	Intrabronchial Valves	Vapor
Studies/patients	1/95	1/350	3/461	5/703	2/350	1/69
Change FEV_1 (%)	+18.9[a]	+0.9	+10.8[a]	+18[a] CF; +2.5 IF	−2.1[a]	+14.7[a]
RV (mL)	—	−40	−320[a]	−580[a]	−380[a]	−300[a]
6MWT (m)	+31	−16	+30.8	+38.1[a]	+19.5[a]	+30.5
SGRQ	−12[a]	−2	−9.1[a]	−7.3[a]	−2.6	−9.7[a]
Mortality (OR)	2.9	0.76	1.49	1.07	4.95	2.82
Adverse events (OR)	3.71[a]	1.33	2.14[a]	5.9[a]	3.41[a]	3.86[a]

Abbreviations: CF, complete fissure; IF, incomplete fissure; OR, odds ratio.
[a] Statistically significant difference versus control group.
Data from van Agteren JE, Hnin K, Grosser D, et al. Bronchoscopic lung volume reduction procedures for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2017;(2):CD012158.

contraindication for coils because the airway bleeding risk is higher.
- Chest x-ray (CXR) is routinely done later in the day after the procedure, to exclude BLVR-related complications, such as pneumothorax.
- The patient remains in observation for at least 24 hours after the intervention.
- Clinically stable patients are then discharged to home rest for the next 48 hours, with slow return to their usual routine to occur in the first 7 days postintervention.
- A follow-up with the pulmonologist 1 month later with standard CXR imaging is arranged.
- Additional clinic follow-up occurs every 6 months for 2 years. Complete pulmonary function tests and diagnostic imaging (CXR or chest CT) are usually part of the clinic visit.
- Patients with optimal clinical response are followed once a year after that.

Most of the current routine follow-up visits follow a strict protocol, either as part of a clinical study or a multicenter registry.

PATIENT SELECTION FOR BRONCHOSCOPIC LUNG VOLUME REDUCTION

Optimal patient selection is a key factor affecting final outcomes. For example, BLVR is contraindicated in patients who suffer frequent moderate COPD exacerbations (>2 per year) because they experience a more rapid decline in quality of life and a worse overall prognosis.[6,40]

It is strongly recommended that evaluation and BLVR treatment be ultimately done by interventional pulmonologists who are experts in the field of LVR.[41]

STEPS IN PATIENT SELECTION

- Obtain basic clinical history and examination.
- Assess expectoration and dyspnea severity using tools, such as mMRC, COPD assessment test, or SGRQ.
- Document frequency of COPD exacerbations in the last 1 year (exacerbations that require antibiotic for symptom resolution).
- Confirm optimal compliance with a pulmonary rehabilitation program in addition to a daily physical activity program.

GENERAL CHARACTERISTICS OF OPTIMAL CANDIDATES FOR BRONCHOSCOPIC LUNG VOLUME REDUCTION

- Symptomatic COPD
- Predominant emphysema phenotype
- mMRC greater than 1
- Two or fewer COPD exacerbations per year
- Severe airflow obstruction as determined by spirometry
- Hyperinflation and air trapping determined by plethysmography
- No smoking for at least 6 months prior to the intervention

Indications and contraindications to BLVR can be seen in **Boxes 1** and **2**.

OBJECTIVE EVALUATION AND WORK-UP

Assessment of Functional Status

Spirometry

Spirometry should confirm an obstructive pattern, with FEV1 within 20% to 50% predicted, and lack of a significant bronchodilator response, defined as change in FEV1 of $\geq$12% to $\geq$200 mL postbronchodilator, to exclude other etiologies of obstruction.

Carbon monoxide diffusion capacity

Should confirm a diffusing capacity of carbon monoxide (DLCO) within 20% to 50% predicted. Avoiding a DLCO less than 20% is recommended based on NETT[7] given the higher complication rate for this group. In the authors' experience, however, and as long as the patient is aware of a possible higher risk, BLVR with coils can still be considered in select patients with DLCO less than 20% because it does not usually affect this value.

Lung volume measurement by plethysmography

TLC greater than 100% and RV greater than 175% are key values when considering BLVR. There are a few considerations about RV:

- Initial studies, such as VENT,[22] suggest an entry cutoff of greater than 150% but recent

Box 1
Inclusion criteria for bronchoscopic lung volume reduction

COPD emphysema phenotype
Nonsmokers (no smoking for at least 6 months)
Optimal medical treatment, including rehabilitation program
FEV_1 (%) 20 to 50
RV (%) >175 to 200
TLC (%) >100
DLCO (%) 20 to 50
6MWT (distance in m) >150
Dyspnea mMRC scale >1

Box 2
Exclusion criteria for bronchoscopic lung volume reduction

- Positive bronchodilator test (increase in FEV_1 by >12% or >200 mL)
- More than 2 COPD exacerbations per year
- Chronic hypercapnia with BiPAP assistance needed (P_{CO_2} >60 mm Hg)
- Previous lung surgery
- Significant comorbidities affecting long-term survival
- Giant bullae corresponding to >1/3 of the total lung volume
- PH with estimated PASP >50 mm Hg (calculated by echocardiography)
- Significant loss of lung parenchyma (FOR COILS ONLY)
- Chronic anticoagulant or antiplatelet treatment (except for low-dose ASA) (FOR COILS ONLY)

expert consensus has recommended a value of at least 175% to 200%.[42]

- For coils, published data suggest that higher RV numbers correlate with better treatment response[30,42] and prospective studies have incorporated an entry RV cutoff of greater than 220%.[31,33]
- In the authors' opinion, BLVR using EBVs can be considered for RV greater than 175% whereas the cutoff for coils should be greater than 200%.

6-minute walk test

The reproducibility of the 6MWT has made it an optimal assessment tool for studies on BLVR. Candidates should be able to walk greater than 150 m during the test.

Diagnostic Imaging

Chest CT is a key test when assessing potential candidates for BLVR to identify contraindications, such as presence of lung fibrosis, suspicious nodules, bronchiectasis, or giant bullae.

In addition to assessing the severity of emphysema, CT helps determine the type of emphysema (centrilobular, paraseptal, or panlobular), distribution (homogeneous or heterogeneous), and fissure integrity. Those findings help determine the type of intervention most likely to be beneficial. For example, cases of panlobular emphysema with significant lung parenchyma destruction should not undergo coils treatment given a higher complication risk. Although the IMPACT study[24] suggested a beneficial effect of EBVs for patients with homogenous emphysema, in the authors' experience, those patients seem to benefit more from coils (compared with EBVs) as long as they fulfill the rest of the selection criteria for BLVR.

The importance of CT assessment has been enhanced with the availability of emphysema quantification software (**Fig. 4**). Quantification software, such as VIDA (VIDA Diagnostics, Cupertino, California)[43] provides information on

- Percentage of emphysema: this is determined using a Hounsfield unit (HU) cutoff of −950 HU, based on 1-mm slices of a high-resolution CT. It also helps determine which lobes are most affected by emphysema.
- Volumetric assessment: estimated by lung and lobes
- Emphysema distribution: heterogeneous emphysema is identified when there is greater than 15% difference in the amount of emphysema between ipsilateral lobes.[44] Less than 15% is considered homogenous emphysema.
- Lung fissures: a fissure is considered complete or intact when at least 85% to 90% of the fissure can be visualized in any of the CT axes. Identification of a complete fissure makes the presence of CV less likely. This increases the chances of an optimal response to BLVR with EBVs because that lobe is more likely to experience complete lobar atelectasis.[23]

Diagnostic Bronchoscopy and Screening for Presence of Collateral Ventilation

Baseline bronchoscopy

The authors recommend a baseline diagnostic bronchoscopy before proceeding with BLVR because

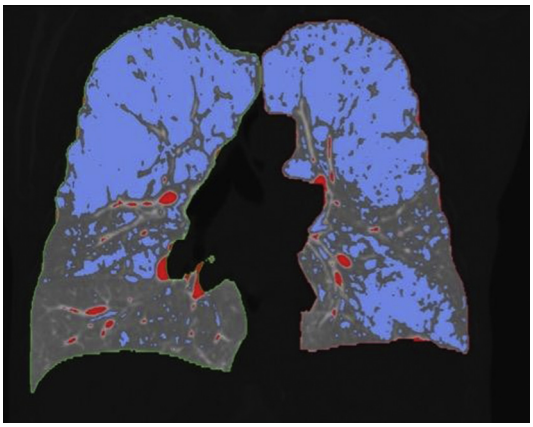

Fig. 4. Emphysema quantification software Syngo. CT Pulmo 3-D. Color blue corresponds to regions of emphysema (−950 HU). (*Courtesy of* Siemens Healthcare GmbH, Erlangen, Germany.)

- It provides information about the bronchial anatomy and identifies possible technical difficulties ahead of BLVR.
- It identifies mucosal or endobronchial lesions not otherwise visible on CT that could contraindicate the BLVR intervention.
- Samples can be obtained for cytology and microbiology. Patients with advanced COPD can have an underlying colonization or indolent infection caused by organisms, such as atypical mycobacteria,[45] which might need to be addressed before proceeding with BLVR.

Evaluation of collateral ventilation

Patients considered for BLVR should also undergo evaluation with the Chartis pulmonary assessment system to functionally exclude the presence of CV. In this study, a catheter with a balloon at the distal tip is passed through the working channel of a 2.8-mm flexible bronchoscope. Once the balloon is inflated at the entrance of the chosen segment or lobe, the airway is blocked for 2 minutes and air from that segment can only flow through the catheter. The Chartis system will then assess expiratory airflow, pressure and resistance. If a steady drop in flow is documented along a simultaneous increase in pressure and resistance, lobar exclusion (ie, absence CV) is confirmed (**Fig. 5**). On the other hand, if airflow remains constant, presence of CV is confirmed (**Fig. 6**). This suggests that the patient is unlikely to benefit from EBV placement.

The authors recommend the routine use of Chartis as part of BLVR evaluation. Given the good correlation between the presence of a complete fissure on CT and absence of CV,[46] however, other experts use evaluation of the fissure on CT as their main tool for CV assessment and use the Chartis system for less straightforward cases.

Evaluation of the pulmonary circulation

Severe COPD can lead to pulmonary hypertension (PH), and PH due to lung disease falls into World Health Organization PH classification group 3.[47] Presence of PH in COPD is associated with symptom worsening, COPD exacerbation risk, and increased mortality.[48,49]

Because of this association and risk, a baseline echocardiogram is mandatory for BLVR candidates. A right heart catheterization is performed when severe PH is suspected or in cases where the echocardiogram are suggestive but inconclusive.

With regard to evaluation of candidates for BLVR, presence of estimated pulmonary arterial systolic pressure (PASP) of greater than 50 mm Hg by echocardiography is considered a contraindication for treatment with both coils and EBVs.[28]

A recent pilot study (6 patients) suggested that placement of EBVs in patients with emphysema and PH was safe.[50] Pulmonary hemodynamic improvement was seen in some of the cases. Because this is the only report suggesting possible safety in this population, BLVR should be contraindicated in the presence of PH. Patients with milder PH could be assessed on a case-by-case basis.

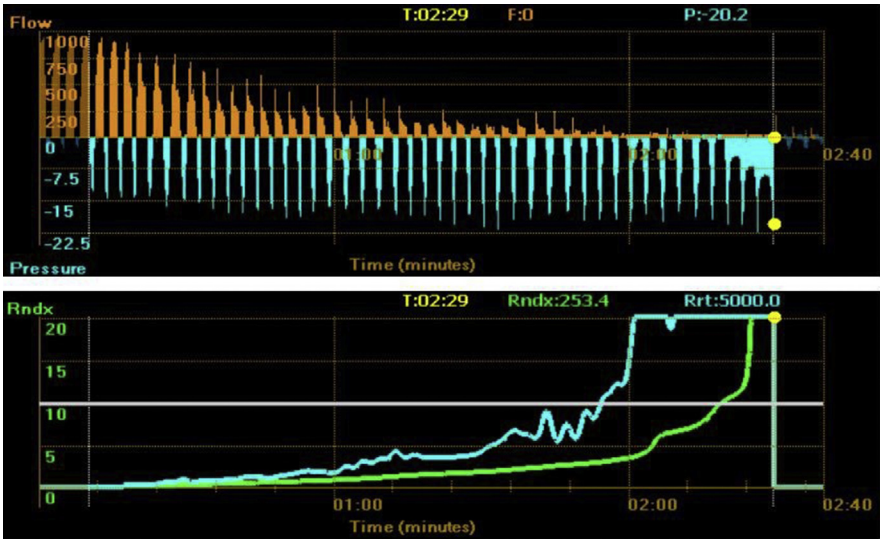

Fig. 5. Upper graph displaying a drop in flow (*orange*) and stable airway pressure (*light blue*). Lower graph displaying an increase in airway resistance (*light blue and green*). Findings are consistent with absence of CV.

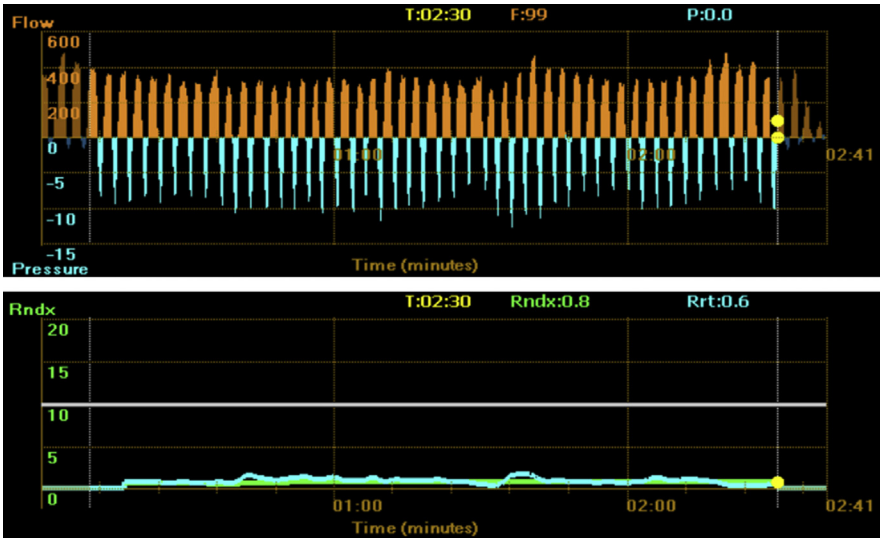

Fig. 6. Upper graph displaying constant flow (*orange*) and pressure (*light blue*). Lower graph displaying no change in airway resistance (*light blue and green*). Findings are consistent with presence of CV.

Other Considerations

During the evaluation of possible candidates, a few other circumstances could contraindicate the procedure besides what was discussed previously, including

- Presence of asymptomatic hypercapnia is not a contraindication per se. It is considered a relative contraindication in those patients who require bilevel positive airway pressure for its management. Severe hypercapnia (>60 mm Hg on room air) is a contraindication for BLVR.[51]
- α_1-antitrypsin deficiency is considered a relative contraindication for BLVR because the procedure can be considered as "compassionate use."
- The use of anticoagulants and antiplatelet drugs in doses higher than 100 mg of ASA is a contraindication to BLVR with coils, given its higher risk for airway bleeding. BLVR candidates who require long-term anticoagulation should then be considered for EBVs instead.
- Patients who have had previous surgical interventions of the lungs or pleural cavities are not considered adequate candidates for BLVR.

BRONCHOSCOPIC LUNG VOLUME REDUCTION DECISION ALGORITHM: COILS VERSUS ENDOBRONCHIAL VALVES

Fig. 7 provides a simplified approach to patient selection for either one of the techniques.

1. Patients fulfill standard criteria for COPD with an emphysema phenotype.
2. Functional testing confirms the severity of the cases.
3. No obvious contraindications are identified (eg, previous pleural interventions, 3 or more COPD exacerbations × year).
4. CT is done to assess the characteristics and distribution of the emphysema and assess fissure integrity.
5. Transthoracic echocardiogram is performed to estimate PASP and assess right heart chambers.
6. A baseline diagnostic bronchoscopy is performed to evaluate the bronchial anatomy and obtain routine samples for microbiology and cytology if needed. Assessment of presence or absence of CV is performed using the Chartis system.
   - If heterogeneous emphysema and lobar exclusion (ie, absence of CV) are documented, EBVs should be considered the first option for BLVR.
   - If homogeneous emphysema and lobar exclusion are confirmed, the authors prefer to proceed with coils as the first option, unless there are contraindications for coils or if there is patient preference for EBVs. Treatment with EBVs is an optimal option as well.
   - If presence of CV is confirmed, the treatment of choice should be coils if no contraindications exist, regardless of the type of emphysema (homogenous or heterogeneous),

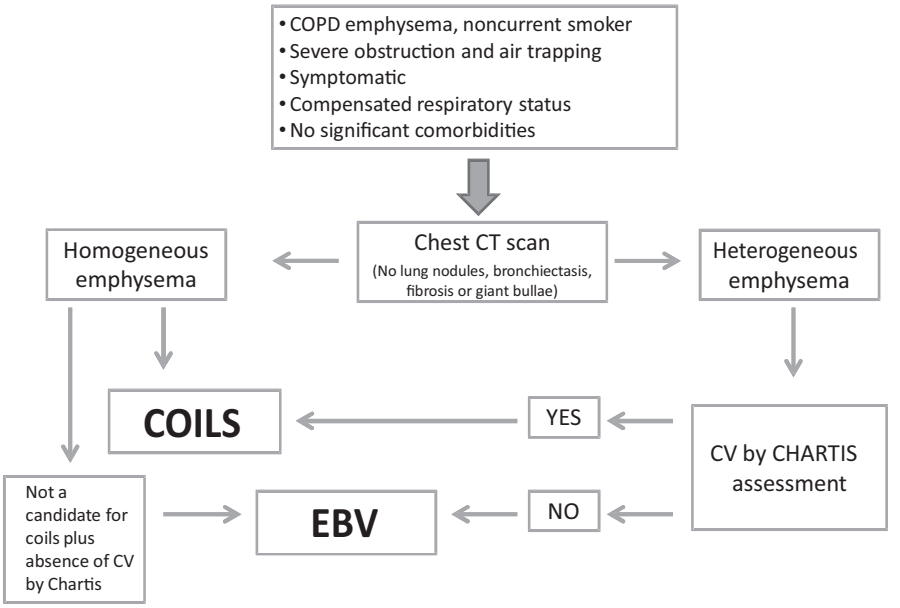

Fig. 7. BLVR algorithm.

SUMMARY

- In a select patient populations, LVR using bronchoscopic techniques has been shown a less invasive and safer option compared with surgical volume reduction data.
- Rigorous patient evaluation and selection by providers with expertise in interventional pulmonology, and BLVR is a key factor to achieve optimal patient outcomes.
- Endoscopic LVR is still in its early stages and it is a rapidly evolving field.
- Although several techniques have been studied for BLVR, unidirectional EBVs and coils are the devices more extensively evaluated. The choice of either one depends on several factors including presence or absence of CV, emphysema characteristics, and patient comorbidities.
- These treatments do not contraindicate evaluation and consideration for lung transplant in patients who continue to decline and fulfill transplant selection criteria.
- These treatment options should be considered and used in addition to a comprehensive and multidisciplinary approach to COPD

REFERENCES

1. Murray CJ, Lopez AD. Measuring the global burden of disease. N Engl J Med 2013;369(5):448–57.
2. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380(9859):2095–128.
3. Kemp SV, Polkey MI, Shah PL. The epidemiology, etiology, clinical features, and natural history of emphysema. Thorac Surg Clin 2009;19(2):149–58.
4. Budweiser S, Harlacher M, Pfeifer M, et al. Co-morbidities and hyperinflation are independent risk factors of all-cause mortality in very severe COPD. COPD 2014;11(4):388–400.
5. Garcia-Rio F, Lores V, Mediano O, et al. Daily physical activity in patients with chronic obstructive pulmonary disease is mainly associated with dynamic hyperinflation. Am J Respir Crit Care Med 2009;180(6):506–12.
6. From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017. Available at: http://goldcopd.org. Accessed June 30, 2017.
7. Fishman A, Martinez F, Naunheim K, et al. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med 2003;348(21):2059–73.
8. Donohue JF. Minimal clinically important differences in COPD lung function. COPD 2005;2(1):111–24.
9. Puhan MA, Chandra D, Mosenifar Z, et al. The minimal important difference of exercise tests in severe COPD. Eur Respir J 2011;37(4):784–90.
10. Jones PW. St. George's respiratory questionnaire: MCID. COPD 2005;2(1):75–9.

11. Hartman JE, Ten Hacken NH, Klooster K, et al. The minimal important difference for residual volume in patients with severe emphysema. Eur Respir J 2012;40(5):1137–41.
12. Kaneda H, Minami K, Nakano T, et al. Efficacy and long-term clinical outcome of bronchial occlusion with endobronchial Watanabe spigots for persistent air leaks. Respir Investig 2015;53(1):30–6.
13. Watanabe Y, Matsuo K, Tamaoki A, et al. Bronchial occlusion with endobronchial Watanabe spigot. J Bronchology Interv Pulmonol 2003;10(4):264–7.
14. Gasparini S, Zuccatosta L, Bonifazi M, et al. Bronchoscopic treatment of emphysema: state of the art. Respiration 2012;84(3):250–63.
15. Shah PL, Slebos DJ, Cardoso PF, et al. Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial): randomised, sham-controlled, multicentre trial. Lancet 2011; 378(9795):997–1005.
16. Koster TD, Slebos DJ. The fissure: interlobar collateral ventilation and implications for endoscopic therapy in emphysema. Int J Chron Obstruct Pulmon Dis 2016;11:765–73.
17. Klooster K, ten Hacken NH, Hartman JE, et al. Endobronchial valves for emphysema without interlobar collateral ventilation. N Engl J Med 2015;373(24): 2325–35.
18. Cetti EJ, Moore AJ, Geddes DM. Collateral ventilation. Thorax 2006;61(5):371–3.
19. 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(4):288–97.
20. 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(6):1319–25.
21. Gillespie CT, Sterman DH, Cerfolio RJ, et al. Endobronchial valve treatment for prolonged air leaks of the lung: a case series. Ann Thorac Surg 2011; 91(1):270–3.
22. Sciurba FC, Ernst A, Herth FJ, et al. A randomized study of endobronchial valves for advanced emphysema. N Engl J Med 2010;363(13):1233–44.
23. Davey C, Zoumot Z, Jordan S, et al. 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(9998):1066–73.
24. Valipour A, Slebos DJ, Herth F, et al. Endobronchial valve therapy in patients with homogeneous emphysema. Results from the IMPACT study. Am J Respir Crit Care Med 2016;194(9):1073–82.
25. Kumar A, Dy R, Singh K, et al. Early trends in bronchoscopic lung volume reduction: a systematic review and meta-analysis of efficacy parameters. Lung 2017;195(1):19–28.
26. Kontogianni K, Eberhardt R. Bronchoscopic Nitinol coil implantation: a new lung volume reduction strategy in COPD. EMJ Respir 2013;1:72–8.
27. Klose H, Achenbach HJ. Rationale for endobronchial coil treatment as the primary intervention for patients with severe emphysema. EMJ Respir 2014;2:74–80.
28. Deslee G, Klooster K, Hetzel M, et al. Lung volume reduction coil treatment for patients with severe emphysema: a European multicentre trial. Thorax 2014;69(11):980–6.
29. Shah PL, Zoumot Z, Singh S, et al. Endobronchial coils for the treatment of severe emphysema with hyperinflation (RESET): a randomised controlled trial. Lancet Respir Med 2013;1(3):233–40.
30. Slebos DJ, Hartman JE, Klooster K, et al. Bronchoscopic coil treatment for patients with severe emphysema: a meta-analysis. Respiration 2015; 90(2):136–45.
31. 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(2):175–84.
32. Redelmeier DA, Bayoumi AM, Goldstein RS, et al. Interpreting small differences in functional status: the six minute walk test in chronic lung disease patients. Am J Respir Crit Care Med 1997;155(4): 1278–82.
33. Sciurba 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(20):2178–89.
34. Reilly J, Washko G, Pinto-Plata V, et al. Biological lung volume reduction: a new bronchoscopic therapy for advanced emphysema. Chest 2007;131(4): 1108–13.
35. Herth FJ, Gompelmann D, Stanzel F, et al. Treatment of advanced emphysema with emphysematous lung sealant (AeriSeal(R)). Respiration 2011; 82(1):36–45.
36. 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(3):651–62.
37. Snell GI, Hopkins P, Westall G, et al. A feasibility and safety study of bronchoscopic thermal vapor ablation: a novel emphysema therapy. Ann Thorac Surg 2009;88(6):1993–8.
38. 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(3):185–93.

39. van Agteren JE, Hnin K, Grosser D, et al. Bronchoscopic lung volume reduction procedures for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2017;(2):CD012158.
40. Miravitlles M, Ferrer M, Pont A, et al. Effect of exacerbations on quality of life in patients with chronic obstructive pulmonary disease: a 2 year follow up study. Thorax 2004;59(5):387–95.
41. Shah PL, Herth FJ, van Geffen WH, et al. Lung volume reduction for emphysema. Lancet Respir Med 2017;5(2):147–56.
42. Eberhardt R, Gompelmann D, Herth FJ, et al. Endoscopic bronchial valve treatment: patient selection and special considerations. Int J Chron Obstruct Pulmon Dis 2015;10:2147–57.
43. Gompelmann D, Eberhardt R, Schuhmann M, et al. Lung volume reduction with vapor ablation in the presence of incomplete fissures: 12-month results from the STEP-UP randomized controlled study. Respiration 2016;92(6):397–403.
44. Herth FJ, Slebos DJ, Rabe KF, et al. Endoscopic lung volume reduction: an expert panel recommendation. Respiration 2016;91(3):241–50.
45. Johnson MM, Odell JA. Nontuberculous mycobacterial pulmonary infections. J Thorac Dis 2014;6(3):210–20.
46. Diso D, Anile M, Carillo C, et al. Correlation between collateral ventilation and interlobar lung fissures. Respiration 2014;88(4):315–9.
47. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013;62(25 Suppl):D34–41.
48. Wells JM, Washko GR, Han MK, et al. Pulmonary arterial enlargement and acute exacerbations of COPD. N Engl J Med 2012;367(10):913–21.
49. Hurdman J, Condliffe R, Elliot CA, et al. Pulmonary hypertension in COPD: results from the ASPIRE registry. Eur Respir J 2013;41(6):1292–301.
50. Eberhardt R, Gerovasili V, Kontogianni K, et al. Endoscopic lung volume reduction with endobronchial valves in patients with severe emphysema and established pulmonary hypertension. Respiration 2015;89(1):41–8.
51. Slebos DJ, Shah PL, Herth FJ, et al. Endobronchial valves for endoscopic lung volume reduction: best practice recommendations from expert panel on endoscopic lung volume reduction. Respiration 2017;93(2):138–50.