

# Bronchoscopic Lung Volume Reduction: A 2018 Review and Update

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## Abstract

Bronchoscopic lung volume reduction (BLVR) procedure has expanded the treatment spectrum of patients with end-stage emphysema. These treatments include valve, coil, thermal vapor ablation, bio-lung volume reduction, targeted lung denervation, and airway bypass stent. This short review provides an up-to-date information on BLVR treatments, their clinical benefits, and an overview of complications. BLVR treatments generally affect dyspnea by reducing hyperinflation and residual volume (RV). Benefits of treatment are associated with improvement in lung function parameters (forced expiration volume in the first second, total lung capacity, RV, and 6-minute walking test) and quality of life. Serious potential pulmonary complications, such as pneumothorax, pneumonia, respiratory failure, and chronic obstructive pulmonary disease exacerbation, may also occur after BLVR treatment. In addition to these, low-cost BLVR methods, such as autologous blood and fibrin glue, are in the developmental stage. Bronchoscopic lung volume reduction treatments are a promising method with positive results for patients with severe emphysema. The widespread use of these techniques, inadequate selection of patients, and non-critical and, therefore, unsuccessful use of BLVR in non-specialist centers lead to a false negative impression of the effectiveness of these techniques. In addition to these considerations, it is obvious that these treatments, which are quite expensive, are burdening social health systems. The reduction of costs or the development of lower-cost treatment methods is important for the future and for the availability of treatments.

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## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airway obstruction with persistent respiratory symptoms and is a relatively treatable disease. Emphysema is one of the most common chronic and progressive conditions associated with COPD. Pathophysiologically, it includes the destruction of the lung parenchyma via chronic inflammation, followed by the permanent enlargement of the terminal bronchioles, dynamic hyperinflation, and loss of elastic recoil, air trapping, and reduced exercise capacity [1]. In addition, there is an increase in residual volume (RV) due to thoracic compression and dysfunction of the respiratory muscles in patients with COPD [2]. Smoking is still the most common cause, and dust exposure and alpha-1 antitrypsin deficiency are also known to be associated with its pathogenesis [3].

At present, standard treatment options include smoking cessation, bronchodilation, mucolytic agents, phosphodiesterase 4 inhibitors, respiratory rehabilitation, and nutritional support, vaccination against influenza and pneumococcus, and long-term oxygen therapy [4]. These treatments help to increase the exercise capacity of patients and decrease symptom exacerbation. However, they do not cure the pathophysiology of the disease or prevent disease progression. In the last decade, in addition to lung volume reduction surgeries (LVRSs), bronchoscopic lung volume reduction (BLVR) has expanded the treatment spectrum of patients with end-stage emphysema [5,6]. These treatments include valve, coil, thermal vapor ablation (TVA), bio-lung volume reduction (BioLVLR), targeted lung denervation (TLD), and airway bypass stent (ABS).

Lung volume reduction surgeries is based on the principle of resecting damaged lung parenchyma and reducing hyperinflation in selected patients with heterogeneous emphysema with upper lobe predominance. Patients are often selected for surgery in accordance with the National Emphysema Treatment Trial (NETT) criteria [5]. Patients with hypercapnic respiratory failure, which is defined as an arterial partial pressure of carbon dioxide (PaCO<sub>2</sub>) >60 mmHg, and oxygen therapy requirement during rest are not recommended for surgery. LVRS can reportedly improve exercise capacity, lung

**Table 1.** General inclusion criteria in the literature

Methods	FEV <sub>1</sub> % pred	RV % pred	TLC % pred	PAB, mmHg	PaCO <sub>2</sub> mmHg	6MWT m	mMRC p	DLCO %	Smoking cessation
Valves <sup>13-20</sup>	15-50	>175	>100	<50	<60	100-500	>2	-	>6 Months
Coils <sup>24-33</sup>	15-45	>175	>100	<50	<55	150-450	-	-	>8 Weeks
TVA <sup>37-39</sup>	20-45	>150 >200*	>100	<35	<55	>140	-	>20	>4 Months
BioLVR <sup>40,41</sup>	<50	>150	>100	<25	<65	>150	-	20-60	>4 Months
TLD <sup>42,43</sup>	30-60	-	-	<25	<60	-	-	-	>6 Months
ABS <sup>44-45</sup>	<50	>180	-	<25	<50	-	>2	>15	>8 Weeks

TVA: thermal vapor ablation; LVR: lung volume reduction; TLD: targeted lung denervation; ABS: airway bypass stent; FEV<sub>1</sub>: forced expiration volume in the 1 s; RV: residual volume; TLC: total lung capacity; PAB: pulmonary arterial pressure; PaCO<sub>2</sub>: arterial partial pressure of carbon dioxide; 6MWT: 6-minute walking test; mMRC: Modified British Medical Research Council; DLCO: diffusing capacity for carbon monoxide; \*: preferably

**Table 2.** Mechanism of the BLVR procedures

	Valve <sup>13-20</sup>	Coil <sup>24-33</sup>	TVA <sup>37-39</sup>	ABS <sup>42,43</sup>	TLD <sup>44,45</sup>
Mechanism	Reducing airway Trapping	Improvement of elastic recoil	Local inflammatory reactions	Blocking Airway	Reduction of bronchoconstriction
Reversibility	Yes	Partial	No	Partial	No
Dependence of collateral ventilation	Yes	No	No	Yes	No
Type of Emphysema	Heterogeneous	Heterogeneous or homogeneous	Heterogeneous, only upper lobe	Homogeneous	Heterogeneous or homogeneous
Possible relevant complications	Pneumothorax, Dislocation, or migration of Valve	COPD Exacerbation, Pneumonia	Local and systemic inflammatory reactions, Pneumonia or Pneumonitis	Exacerbation, pneumothorax, hemoptysis	Exacerbation, Procedure related

BLVR: bronchoscopic lung volume reduction; TVA: thermal vapor ablation; LVR: lung volume reduction; TLD: targeted lung denervation; ABS: airway bypass stent

function, and quality of life, especially in patients with upper lobe emphysema [5]. However, patient selection is limited due to high postoperative non-fatal pulmonary complications and short-term mortality of 6.9% [5]. In addition to medical treatment and surgery, BLVR treatments, especially in specific types of patients, have reportedly yielded promising short- to medium-term results [6-10]. After these results, the BLVR treatment methods (valve and coil) were introduced into the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 guideline [4]. The guideline states that LVRS or BLVR treatments can be considered only in a refractory situation to optimal medical treatment. However, it has been reported that patients who are not eligible for both treatment methods may be candidates for lung transplantation if their forced expiration volume in the first second (FEV<sub>1</sub>) values are <25% [4].

This short review provides an up-to-date information on BLVR treatments, their clinical benefits, and an overview of complications. All bronchoscopic approaches are presented here.

**BRONCHOSCOPIC APPROACH TO LUNG VOLUME REDUCTION**

Owing to the high complication rate and risk of mortality observed during the NETT trial, in recent years, less invasive

emphysema treatment procedures and bronchoscopic approaches have been developed [5]. These methods have been proven effective and safe in the short- to medium-term clinical trials [6-10]. Studies investigating long-term results are ongoing. The indications, effect mechanisms, outcomes, and complication rates of these BLVR treatment modalities are discussed further below.

**COMMON INDICATIONS**

Patients tend to exhibit the same typical indications, with some variation in minor details. In general, they include evidence of emphysema diagnosed via computed tomography, post-bronchodilator FEV<sub>1</sub> <15%-50% predicted, RV >175%, total lung capacity (TLC) >100%, 6-minute walking test (6MWT) >150 m, pulmonary hypertension not present, PaCO<sub>2</sub> <50-55 mmHg, and cessation of smoking >2 months prior [6]. Table 1 shows the generally accepted indications pertaining to all BLVR techniques.

**MECHANISM**

BLVR treatments generally affect dyspnea by reducing hyperinflation and RV. Individually, they have different mechanisms of action and are not suitable for every patient. Endobronchial valves (EBVs) reduce air trapping, coils improve the elastic

**Table 3.** Overview of principal BLVR-Valve Studies

Study / Author	Year	n	Follow-up time, M	$\Delta$ FEV <sub>1</sub>	$\Delta$ RV L	$\Delta$ 6MWT m	$\Delta$ SGRQ point	TLVR mL
Sciurba et al. [14]	2010	220	6	+34.5 mL, +4.3%	*	+9.3	-2.8	*
Herth et al. [15]	2012	111	12	+15.0%	*	+22%	-5.0	*
Davey et al. [16]	2015	25	6	+60 mL, +8.7%	-0.26	+25.0	-4.4	*
Valipour et al. [17]	2016	43	3	+100 mL	-0.42	+22.6	-8.6	-1195
Klooster et al. [18]	2017	64	12	+17.0%	-0.68	+61.0	-11.0	*
Fiorelli et al. [19]	2017	33	60	+17.0%	-39%	+91.0	-17.0	*
Kemp et al. [20]	2017	65	6	+140 mL, +20.7%	-0.66	+36.2	-7.2	*
Welling et al. [13]	2018	318	6	+53.4 mL	-0.20	*	-4.3	-463

  

Overview of Complications								
Study / Author	Year	n	Follow-up, M	Pneumonia	COPD Exc.	PNX	Valve EMR	Death
Sciurba et al. [14]	2010	220	6	3.2%	9.3%	4.2%	*	0.9%
Herth et al. [15]	2012	111	12	11.7%	42.3%	8.0%	*	5.4%
Davey et al. [16]	2015	25	6	8.0%	64.0%	8.0%	20.0%	8.0%
Valipour et al. [17]	2016	43	3	0	16.3%	25.6%	7.0%	0
Klooster et al. [18]	2017	64	12	8.0%	14.0%	22.0%	17.0%	3.0%
Fiorelli et al. [19]	2017	33	60	3.0%	*	6.0%	5.0%	0
Kemp et al. [20]	2017	65	6	4.6%	4.6%	29.2%	1.5%	1.5%

n: patient population; M: month; TLVR: target lobar volume reduction; SGRQ: St George's Respiratory Questionnaire total score; COPD: chronic obstructive pulmonary disease; Exc: Exacerbation; PNX: pneumothorax; EMR: Expectoration, migration, and replacement; FEV<sub>1</sub>: forced expiration volume in the 1 s;  $\Delta$ : change; \*: no data

recoil of the lungs, BioLVR and TVA create a local inflammatory reaction, ABS blocks the airway, and TLD reduces bronchoconstriction through innervation (Table 2) [6].

### Endobronchial Valves Implantation

Endobronchial valves (Spiration, Inc., Redmond, WA, USA) are inserted bronchoscopically into the targeted segmental or subsegmental bronchi. With regard to blocking, they only allow a unidirectional flow of air during expiration, so that the treated lung section is vented, and the following atelectasis formation achieves the desired volume-reducing effect. The procedure can be performed under mild sedation as a standard bronchoscopic intervention. Patients with collateral ventilation or parenchymal connections in the relevant lung lobe are not suitable for this procedure. If collateral ventilation (short-circuit connection) is present, the desired atelectasis does not occur in the targeted lobe after valve insertion. With planned valve therapy, the likelihood of a good response to therapy by computed tomographic analysis may indicate completeness of interlobar fissures, and/or the direct determination of collateral ventilation with the Chartist system can be estimated during bronchoscopy [11,12].

Bronchoscopic valve application aims to achieve targeted lobar volume reduction (TLVR) in patients with severe emphysema and is considered an efficacy parameter. In this respect, a quantitative multidetector computed tomography scan is used to calculate and analyze efficacy, and currently, a 350 mL reduction is considered indicative of a favorable response [13]. Nevertheless, the importance of TLVR after valve implantation is unclear.

Several randomized controlled trials have confirmed the efficacy of EBV treatment [13-20]. Efficacy has been assessed via changes in lung function parameters, exercise tests, and health-related quality of life questionnaires, such as the St. George's Respiratory Questionnaire (SGRQ) [20], and significant improvements have been reported. Studies conducted from 2010 to 2017 collectively indicate that the mean FEV<sub>1</sub> increases to 77.5 mL (34.5-140 mL) and 13.7% (4.3%-20.7%), the mean RV decreases to 440 mL (200-680 mL), and the mean 6MWT increases to 40.8 m (9.3-91.0 m) (Table 3) [13-20].

In the previous studies, the mean survival after EBV treatment was 51 (46.5-56.3) months, and the death rate was 27% (9/33 patients) in the longest follow-up study. The causes of death reported were cancer, myocardial infarction, and end-stage respiratory failure [15]. Another interesting study has reported the 10-year survival results of patients with EBV treatment between 2002 and 2004. In that study, 19 patients were examined, and 40% of patients with atelectasis and 14% of patients without atelectasis were alive. In addition, attention has been drawn to the future development of collateral ventilation in patients and, if necessary, the replacement of EBVs [21].

Notably, however, EBV treatment is also associated with some risk. Data related to complications in published studies include COPD exacerbation rates of 9.3%-64.0%, pneumonia rates of up to 11.7%, pneumothorax rates of 4.2%-29.2%, valve migration and replacement rates of 1.5%-20.0%, and mortality rates of up to 8%. Another less frequent and important complication is granulation formation around the valves and associated EBV dislocation (Table 3) [13-20].

Finally, the EBV procedure is relatively expensive. Depending on the relevant agreements with local commercial and social health systems, the cost of the Chartis catheter and the delivery system for a single procedure range from €8,200 to €9,200. This does not include any costs associated with the actual performance of the operation itself or the management of any complications should they arise. It is a current challenge for both healthcare systems and valve manufacturing companies to make this treatment more accessible in developing countries [22].

### Endobronchial Coil Implantation

Coil treatment (PneumRx, Inc., Mountain View, CA, USA) has been developed for patients with interlobar collateral ventilation in the years following EBV therapy. A pilot study of 22 BLVR operations published by Herth et al. [23] in 2010 was successful, and the treatment was reported to be more useful in heterogeneous emphysema.

Over the years, there have been improvements in procedures and techniques, and it is generally considered acceptable practice for a patient to undergo bronchoscopic placement of 8-14 coils (mean number of 10 coils) in one lung under general anesthesia and fluoroscopy [24,25]. Depending on the anatomical length of the subsegment, 100, 125, and 150 mm coils are preferred. In general, each subsegment has 1 coil implant, with an average of 10 coils per lobe. Although the middle lobe and lingual segment are generally not preferred for treatment, it is necessary for the patient to have intact parenchymal tissue in unintended lung areas. Emphysema in patients is confirmed via high-resolution computed tomography (HRCT), with the required lung function parameters of FEV<sub>1</sub> 15%-45%, RV >175%, TLC >100%, and 6MWT 150-450 m. The treatment method is not recommended for patients who are active smokers or patients with paraseptal emphysema, pulmonary arterial pressure (PAP) >50 mmHg, bronchiectasis, lung cancer, or bullous lesions >4 cm. It is also not recommended for patients undergoing anticoagulation therapy, though in such cases, the treatment may be feasible in conjunction with the implantation of left atrial appendage occlusion and subsequent anticoagulation reduction.

The principle of the coils is simple. The implanted wire spirals collect the diseased lung tissue, creating more space for less diseased tissue in the surrounding region. This enhances the capacity for respiratory function, the natural elasticity of the lung improves, and the lungs can stretch and contract better during the breathing process. As a result, this alleviates respiratory distress in patients. Studies conducted from 2012 to 2018 indicate that the average FEV<sub>1</sub> increases to 130 mL (90-200 mL) and 12.1% (7%-14%), the average RV decreases to 420 mL (310-510 mL) and 16.5% (14.5%-22.0%), and the mean 6MWT increases to 47 m (14.6-84.0 m) (Table 4) [24-33].

Complications may also ensue immediately or after treatment using this treatment method. The complication rates in published studies include COPD exacerbation of 41.0% (10.8%-87.0%), pneumonia of 14.8% (0%-46.0%), pneumothorax of 5.7% (0%-11.6%), and mortality of 3.3% (0%-8%). Another less frequent complication is pleuritic chest pain and hemoptysis after treatment (Table 4) [24-33].

The total costs for 1 year are \$53,521 for BLVR coil treatment and \$5912 for follow-up patients only [30]. Based on one preliminary study (REVOLENS) of patients with severe emphysema followed up for 6 months, the initial cost of BLVR coil treatment appears to be high, but it seems that large-scale studies are needed to determine its long-term cost and effectiveness [30].

### Thermal Vapor Ablation

In addition to coils and EBVs, other endoscopic options for reducing lung volume have been developed. Bronchoscopic TVA (Uptake Medical Corporation, Seattle, WA, USA) is one of the techniques. It delivers thermal energy directly to the airways via a bronchoscope through heated water vapor. It induces an inflammatory reaction by instilling water vapor into the destroyed lung parenchyma. The local inflammatory reaction leads to fibrosis and scarring after approximately 8-12 weeks and thus to the desired lung volume reduction. This irreversible procedure is only preferred in patients with upper lobe emphysema, regardless of collateral ventilation [34,35]. The instillation of a hot water vapor at 75°C occurs via a special balloon catheter, with which the lung area to be treated is occluded. The vapor dose is calculated based on the mass of the lung tissue to be treated, and the average vapor dose is 10 cal/g alveolar tissue. This makes the targeted treatment of the area selected based on the HRCT possible. The heterogeneity index (HI) was identified as a predictor of an excellent outcome following bronchoscopic TVA. Patients with heterogeneous disease with an HI >1.2 and patients with COPD GOLD IV had greater improvements in FEV<sub>1</sub> and 6MWT in recent studies [34,35].

The criteria in defining patients who can be treated in principle are (1) upper lobe dominant emphysema determined via HRCT; (2) ages between 40 and 75 years; (3) FEV<sub>1</sub> between 15% and 45% predicted; (4) RV >150% predicted, ly >200; (5) TLC >100% predicted; (6) diffusing capacity of the lungs for carbon monoxide (DLCO) >20% predicted; (7) 6MWT >140 m; (8) PaCO<sub>2</sub> <55 mmHg and partial arterial oxygen pressure >45 mm Hg; and (9) non-smoker for ≥4 months. Bronchoscopic TVA treatment is not recommended for patients with (1) known  $\alpha$ -1-antitrypsin deficiency, asthma, or bronchiectasis; (2) bulla >1/3 lobe of the lung; (3) history of thoracotomy; (4) left ventricular ejection fraction ≤40%; or (5) pulmonary hypertension (mean pulmonary artery pressure ≥35 mmHg) [36].

There are fewer published TVA studies than published studies pertaining to coils and EBVs. Two major TVA studies conducted from 2012 to 2016 showed reduced hyperinflation and dyspnea and improvement of exercise tolerance and health-related quality of life. The first study was an uncontrolled follow-up study in which unilateral bronchoscopic thermoablation with a vapor dose of 10 cal/g was performed in 44 patients with an HI of >1.2. After 6 months of treatment, there was a 48% decrease in lobar lung volume and a significant improvement in lung function parameters and quality of life. There were also significant improvements in FEV<sub>1</sub> (0.14±0.16 L), RV (-0.40±0.71 L), 6MWT (46.5±67.1 m), and SGRQ (-14±15.1 points) at a 6-month interval. A GOLD IV subgroup shows greater improvements than GOLD III [37]. The second study was the first randomized con-

**Table 4.** Overview of principal BLVR-Coil Studies

Author	Year	n	Follow-up, M	$\Delta$ FEV <sub>1</sub>	$\Delta$ RV	$\Delta$ 6MWT	$\Delta$ SGRQ
Slebos et al. [24]	2012	16	6	+14.9%	-11.4%	+84.4 m	-14.9
Shah et al. [25]	2013	23	3	+14.1%	-0.51 L	+51.1 m	-8.6
Klooster et al. [26]	2014	10	6	+0.11 L	-22.0%	+61.0 m	-15.0
Deslee et al. [27]	2014	34	12	+16.0%	-13.75%	+51.4 m	-11.1
Hartman et al. [28]	2014	35	12	+0.20 L	-21%	+31.0 m	-4.2
		27	24	-0.05 L	-10%	-12.0 m	-8.0
		22	36	-0.04 L	-2%	-31.5 m	-7.2
Zoumot et al. [29]	2015	35	12	+8.9%	-0.32 L	+34.1 m	-6.1
Deslee et al. [30]	2016	50	12	+0.09 L	-0.52 L	+9%	-11.1
Sciurba et al. [31]	2016	158	12	+7.0%	-0.31 L	+14.6 m	-8.9
Gülşen et al. [32]	2017	40	6	+0.15 L	-14.5%	+48.0 m	-10.4
Simon et al. [33]	2018	33	3	+0.10 L	-0.44 L	+48.0 m	*

**Overview of Complications**

Author	Year	n	Follow-up, M	Pnx	COPD Exc.	Pneumonia	Death
Slebos et al. [24]	2012	16	6	0	87.0%	18.7%	0
Shah et al. [25]	2013	23	3	8.6%	17.0%	0	0
Klooster et al. [26]	2014	10	6	10%	70.0%	0	0
Deslee et al. [27]	2014	34	12	11.6%	33.0%	23.3%	0
Hartman et al. [28]	2014	35	12	6.0%	51.0%	46.0%	3%
		27	24	0	37.0%	7.0%	8%
		22	36	0	36.0%	5.0%	6%
Zoumot et al. [29]	2015	84	12	9.6%	10.8%	2.4%	-
Deslee et al. [30]	2016	50	12	2.0%	26.0%	18.0%	8%
Sciurba et al. [31]	2016	158	12	9.7%	27.7%	20.0%	6.5%
Gülşen et al. [32]	2017	40	6	0	41.4%	17.0%	2%
Simon et al. [33]	2018	33	3	0	46.3%	5.6%	0

n: patient population; COPD: Chronic obstructive pulmonary disease; FEV<sub>1</sub>: forced expiration volume in the 1 s;  $\Delta$ : change; M: month; SGRQ: St George's Respiratory Questionnaire total score

trolled trial of TVA treatment ( $n=46$ ) versus medical management ( $n=24$ ) and reported mean relative improvements of 14.7% (7.8%-21.5%) and 0.13 L (0.063-0.198 L) in FEV<sub>1</sub>, -9.7 points (-15.7 to -3.7 points) in SGRQ, and 30.5 m (1.5-62.4 m) in 6MWT at a 6-month follow-up [38].

The most common complication in the first few weeks was an excessive inflammatory response characterized by respiratory symptoms, such as dyspnea, cough, fever, and mild hemoptysis [39]. The most common complications in the following period were pneumonia (18%-23%) and COPD exacerbation (9%-24%) (Table 5). Therefore, consistent inpatient follow-up and concomitant prophylactic antibiotic and anti-inflammatory therapy are required. The severity of the local inflammatory response correlates with the good response to thermoablation and better result [34]. More effective TVA is associated with more pronounced inflammation. In addition, there appears to be a correlation between the volume of the treated lung lobe and the extent of the inflammatory response. Patients with a treated lung volume of >1700 mL had to be re-hospitalized more frequently during the course of the disease due to a pronounced local inflammatory response. However, 6 months after TVA, this patient population exhibited the greatest benefit from TVA.

**Bio-Lung Volume Reduction**

BioLVR or polymeric LVR is a method of bronchoscopic instillation of hydrogel into the target lobe that is intended to block lung tissue in patients with advanced emphysema. AeriSeal (Aeris Therapeutics, Inc., Woburn, MA, USA) is a foam-like liquid medium used in bronchioles and alveoli with 10 mL (low dose) or 20 mL (high dose) for each part. The application of the polymer foam is an irreversible BLVR procedure. Bronchoscopically applied polymer resin causes fibrosis in the targeted pulmonary parenchyma. A subsequent inflammatory reaction functions to decrease the tissue in the target regions and reduce volume. In the first study, which included 14 patients and was published in 2011, a positive therapeutic effect was apparent but so were complications, mainly due to inflammatory processes [40]. The results reported included an FEV<sub>1</sub> increase of +15.9% predicted, a 6MWT increase of 28.7 m, RV/TLC change of -7.4% predicted, forced vital capacity (FVC) increase of 24.1% predicted, DLCO change of +9.3%, and SGRQ score change of -9.9 points [40].

In the "ASPIRE" study conducted in 2014, BioLVR using hydrogel was compared with medical therapy and has since been abandoned due to increased adverse events and an unacceptable complication rate resulting in patients with

**Table 5.** Overview of principal Thermal Vapor Ablation Studies

Author	Year	n	Follow-up, M	Δ FEV <sub>1</sub> mL	Δ RV mL	Δ 6MWT m	Δ SGRQ point	TLVR mL
Herth et al. [37]	2012	22	12	+64 <sup>£</sup>	-270 <sup>£</sup>	+10.9 <sup>£</sup>	9.4 <sup>£</sup>	-735 <sup>£</sup>
		22	12	+108 <sup>†</sup>	-335 <sup>†</sup>	+25.6 <sup>†</sup>	-12.7 <sup>†</sup>	-772 <sup>†</sup>
Gompelmann et al. [35]	2014	44	6	+141	-406	*	*	-716
Gompelmann et al. [39]	2016	35	12	+65	-108	6.2	-12.1	*
Herth et al. [38]	2016	45	6	+130	-302	30.5	-9.7	*

  

Overview of Complications								
Author	Year	n	Follow-up, M	Pneumonia or pneumonitis	COPD Exc.	PNX	SAEs	Death
Gompelmann et al. [39]	2016	35	12	23.0%	9.0%	3.0%	26.0%	3.0%
Herth et al. [38]	2016	45	6	18.0%	24.0%	2.0%	36.0%	2.0%

SAEs: serious adverse events; \*: COPD Gold III patients; £: COPD Gold III patients; †: COPD GOLD IV patients; n: patient population; M: month; TLVR: target lobar volume reduction; FEV<sub>1</sub>: forced expiration volume in the 1 s; Δ: change; 6MWT: 6-minute walking test

BioLVR requiring more hospitalization [41]. The clinical method it entails is currently not recommended.

### Targeted Lung Denervation

Targeted Lung Denervation is the most recently developed novel therapeutic COPD treatment. Technically, it is not a volume reduction procedure; rather, its aims are ablation of parasympathetic nerves innervating the basal lung and the reduction of bronchoconstriction. Its effects are similar to those of anticholinergic drugs. It is performed via a double-cooled radiofrequency catheter (Holaira, Minneapolis, MN, USA). Radiofrequency (15-20 W) is applied to the target lung and 8 points. The cooler is also used in order to prevent the resulting heat from affecting the inner surface of the airway. It is usually applied bilaterally and step by step. Slebos et al. [42] conducted an initial pilot study in 2015 and reported that 20 W is more successful than 15 W. Patients receiving TLD incorporating 20 W reported an increase of 11.6% in FEV<sub>1</sub>, an increase of 6.8 min in submaximal cycle endurance, and a decrease of 11.1 points in SGRQ score. The most frequent adverse event at a 1-year follow-up was COPD exacerbation (59%). Gastritis (18%), respiratory inflammation (18%), and anaphylactic reaction (5%) were also observed. Non-serious complications, such as bronchial perforation, ulceration, and stenosis, may also rarely occur depending on the procedure. In another study, the anti-inflammatory effects of TLD were reported, and it was asserted that further research is needed [43].

The major criteria in defining patients who can be treated in principle are (1) age ≥40 years; (2) COPD with FEV<sub>1</sub>/FVC <70% and FEV<sub>1</sub> between 30% and 60% predicted; (3) positive relative change in FEV<sub>1</sub> >15% following inhalation of ipratropium; (4) non-smoking for ≥6 months; (5) smoking history of at least 10 pack-years; and (6) PaCO<sub>2</sub> <60 mmHg, PaO<sub>2</sub> >55 mmHg, and PAP <25 mmHg [42]. The first prospective randomized controlled trial of lung denervation ("AIRFLOW-1", NCT02058459) is still ongoing. TLD is not yet used in routine clinical practice.

### Airway Bypass Stent

ABS (Broncus Technologies, Inc., Mountain View, CA, USA) is only recommended for patients with severe homogeneous

emphysema. In this method, extra-anatomical transitions are made from the airway walls to the lung parenchyma to release the trapped air. A small drug (paclitaxel)-eluting stent is inserted into each drilled hole so that bypass occlusion is avoided. The intention is to bypass small collapsed airways. However, studies and data on this treatment method are limited, and this BLVR technique is still in the trial phase.

In a small study reported by Choong et al. [44] in 2009, ABS improved pulmonary function parameters and reduced respiratory distress. However, no statistically significant results were obtained. In 2011, the "EASE" study involving 315 patients with severe homogeneous emphysema was reported [45]. Patients were randomly assigned to the ABS group (n=208) or the control group (n=107), followed by 1, 3, 6, and 12 months of respiratory function parameter assessment, 6MWT, and SGRQ. There was no statistically significant difference between the two groups detected in their study. Compared with baseline, there was an increase of 12% in FEV<sub>1</sub> and 1 point in the modified British Medical Research Council scale 6 months after the procedure. Therefore, it was reported that ABS is effective in the short term. Loss of efficacy over time is thought to be due to factors involving mucus plugs and granuloma formation. For this reason, it has been stated that further research is required in order to optimize the treatment method, and it is currently not one of the preferred BLVR treatments in practice.

### Bronchoscopic Lung Volume Reduction Using Autologous Blood and Fibrin Glue

A pilot study reported in 2016 assessed the efficacy and safety of BLVR using low-cost agents including autologous blood (n=7) and fibrin glue (n=8) [46]. On week 12 after the procedure, the autologous blood group exhibited an 8% FEV<sub>1</sub> increase and a 16 m 6MWT increase, whereas the fibrin glue group exhibited a 17% FEV<sub>1</sub> increase and a 96 m 6MWT increase. One patient in the autologous blood group had pneumonia in the first 10 days after the procedure, and one patient in the fibrin glue group had exhibited COPD exacerbation at 12 weeks follow-up, and mortality was not reported. The method was shown to constitute an effective and safe treatment, with good cost effectiveness for patients with severe

**Table 6.** Overview of benefits of all BLVR techniques in the literature

Technique	$\Delta$ FEV mL	$\Delta$ FEV % pred.	$\Delta$ RV mL	$\Delta$ RV % pred.	$\Delta$ 6MWT m
Valve	77.5 (34.5-140)	13.7 (4.3-20.7)	440 (200-680)	-	40.8 (9.3-91.0)
Coil	130 (90.0-200)	12.1 (7.0-14.0)	420 (310-510)	16.5 (14.5-22.0%)	47.0 (14.6-84.0)
TVA	101 (64.0-141)	-	284 (108-406)	-	18.3 (6.2-30.5)

  

Overview of all mean complication rates					
Technique	Pneumonia	COPD Exacerbation	PNX	Migration and replacement	Death
Valve	6.4 (0-11.7)	25.0 (4.6-64.0)	14.7 (4.2-29.2)	10.1 (1.5-20.0)	2.6 (0-8.6)
Coil	14.8 (0-46.0)	41.0 (10.8-87.0)	5.7 (0-11.6)	-	3.3 (0-8.0)
TVA	21.0 (18-23.0)	16.5 (9.0-24.0)	2.5 (2-3.0)	-	2.5 (2-3.0)

Data of benefits are shown mean (min-max)/Data of complications are shown mean % (min-max)

COPD: chronic obstructive pulmonary disease; FEV: forced expiration volume;  $\Delta$ : change; M: month; PNX: pneumothorax; 6MWT: 6-minute walking test

emphysema. This biological lung volume reduction treatment is very promising in terms of its low-cost. Notably, however, the very small sample size and short follow-up detract from the power of the study. There is a need for long-term studies of cost, effectiveness, and safety in relation to this method.

#### REVERSIBILITY OF ALL BRONCHOSCOPIC LUNG VOLUME REDUCTION PROCEDURES

Reversibility of treatments and informing patients in this regard is a very important issue. EBV treatments are generally considered reversible, whereas TLD and TVA are irreversible. The coil procedure is regarded as partially reversible. Only three studies in the literature describe the removal of the coils. In a small case series (n=3) of patients with pleuritic pain, the coils could be removed within 4 weeks after implantation [47]. In another study, persistent thoracic pain was reported after treatment, and two coils were removed after 10 months [48]. Gülşen et al. [32] removed and replaced the coil in 10% of the patients during the procedure. Thus, the literature suggests that the removal of the coils is generally only possible during the procedure and in the following few months, and that it is not possible to remove all coils.

#### BENEFITS OF BRONCHOSCOPIC LUNG VOLUME REDUCTION METHODS

With regard to the benefits of treatment, EBV is associated with average increases of 77.5 mL (34.5-140.0 mL) in FEV<sub>1</sub> and 40.8 m (9.3-91.0 m) in 6MWT and an average reduction of 440 mL (200-680 mL) in RV. Coil therapy reportedly results in average increases of 130 mL (90-200 mL) in FEV<sub>1</sub> and 47.0 m (14.6-84.0 m) in 6MWT and an average reduction of 420 mL (310-510 mL) in RV. TVA treatment results in average increases of 101 mL (64-141 mL) in FEV<sub>1</sub> and 18.3 m (6.2-30.5 m) in 6MWT and an average reduction of 284 mL (108-406 mL) in RV (Table 6).

#### COMPLICATIONS OF BRONCHOSCOPIC LUNG VOLUME REDUCTION TREATMENT AT A GLANCE

Serious potential pulmonary complications are associated with BLVR treatment methods. The complications of EBV treatments most commonly reported in the literature are COPD exacerbation (25.0%; 4.6%-64.0%) and pneumotho-

rax (14.7%; 4.2%-29.2%). In this treatment method, valve migration is reportedly seen in approximately 10.1% (1.5%-20.0%) of the patients. Coil treatments are most commonly associated with COPD exacerbation (41.0%; 10.8%-87.0%), pneumonia (14.8%; 0%-46.0%), and pneumothorax (5.7%; 0%-11.6%). In TVA treatments, the most common complications are pneumonia (21.0%; 18.0%-23%) and COPD exacerbation (16.5%; 9.0%-24.0%). The mortality rates are reportedly 2.6%, 3.3%, and 2.5%, respectively (Table 6).

#### POST-TREATMENT OF ACUTE INFLAMMATORY RESPONSE

Bronchoscopic Lung Volume Reduction treatments generally induce an acute inflammatory response (fever, dyspnea, cough, chest pain, and/or elevated inflammatory markers) after treatment. The authors generally recommend and administer steroid and prophylactic antibiotic therapy for 7 days to reduce inflammation. In addition, it is advisable to monitor patients in the hospital for at least 1 night and administer prophylactic non-steroidal anti-inflammatory drugs and stress ulcer prophylaxis for 3 days after treatment [49,50]. Although there is no general consensus on the application of prophylactic antibiotics, they are commonly used by the authors due to the high risk of COPD exacerbation and pneumonia. Pneumococcal and influenza vaccines are an overlooked but absolutely necessary consideration in these patients.

#### ONGOING AND FUTURE STUDIES

There are many future studies of BLVR techniques planned. The most interesting are the "BREATHE-NL" study in which a 5-year efficacy and benefit of EBV treatments was planned, the "LVRC-Micro Study" in which changes in the microbiome of the lungs will be observed after BLVR coil treatment, the study of sleep quality in coil therapy, the 3-year effects of TLD treatment, the "AIRFLOW-1 Study" to investigate the 3-year effects and benefits of TLD treatment, and the "BLOOD-VALVES Study" to compare EBV with low-cost autologous blood (Figure 1).

#### CONCLUSION

BLVR treatments are a promising method with positive results for patients with severe emphysema. Optimal patient and method selection for BLVR treatments and implementation in

Study	Technique	Estimated completion year	Trial Number	n	Outcome	Follow-up
LIBERATE	Valve	11/2022	NCT01796392	190	Medium-term efficacy	1 year
BEVA	Valve	12/2020	NCT03264768	40	Short term efficacy	6 month
BREATHE-NL	Valve	09/2026	NCT02815683	500	Long-term efficacy and effect	5 year
LVRC-Micro	Coil	01/2019	NCT03010566	30	Change in the microbiome	6 month
Franke et al.	Coil	03/2018	NCT02399514	20	Sleep Quality	1 year
AIRFLOW	TLD	11/2019	NCT02058459	140	Long-term efficacy	3 year
DISCOVER	TLD	09/2021	NCT03213080	200	Long-term efficacy	2 year
BLOOD-VALVES	EBV vs. autologous blood	02/2020	NCT03010449	20	Short-term efficacy and comparison of costs	6 month

**Figure 1.** Ongoing randomized clinical trials of bronchoscopic lung volume reduction therapies

experienced centers are very important. However, it is necessary to be prepared for potential complications. The widespread use of these techniques, inadequate selection of patients, and non-critical and therefore, unsuccessful use of BLVR in non-specialist centers lead to a false negative impression of the effectiveness of these techniques. In addition to these considerations, it is obvious that these treatments, which are quite expensive, are burdening social health systems. The reduction of costs or the development of lower-cost treatment methods is important for the future and for the availability of treatments. Therefore, BLVR in patients with severe emphysema will be a treatment of choice in the near future once clinical trials show the ongoing long-term effectiveness of the procedures.

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