Review Article

Bronchoscopic interventions for emphysema: Current status

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ABSTRACT

Chronic obstructive pulmonary disease is a prevalent and progressive disease. The recently developed bronchoscopic lung volume reduction (BLVR) techniques offer personalized therapeutic options in subgroups of patients with severe emphysema. Endobronchial and intrabronchial valves (EBV/IBV) achieve lung volume reduction by lobar atelectasis. The lung volume reduction coils (LVRCs) and bronchoscopic thermal vapor ablation (BTVA) induce tissue compression, either mechanically or through inflammatory processes. While the effects of EBV/IBV are reversible by removing the implants, the effects of LVRC are partially reversible and that of BTVA is irreversible. The presence of interlobar collateral ventilation (CV) impacts on EBV/IBV treatment outcome due to its mechanism of action. Therefore, using radiological and endoscopic techniques to assess CV has a vital importance. Current evidence of BLVR demonstrates acceptable safety and short-term clinical efficacy. However, head-to-head trials are lacking, and further research is needed to establish long-term clinical benefit, durability, and cost-effectiveness of these techniques.

KEY WORDS: Bronchoscopic lung volume reduction, bronchoscopic thermal vapor ablation, endobronchial valve, intrabronchial valve, lung volume reduction coil

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a prevalent lung disease that affects 251 million people and accounts for 5% of all deaths globally.[1,2] It is a chronic respiratory disease with a high burden across many regions worldwide and impacts significantly on morbidity and mortality.[3-6] COPD is a heterogeneous and progressive disease that involves a spectrum of pathophysiological mechanisms including destruction of alveoli and lung parenchyma (emphysema) and small airway inflammation (obstructive bronchiolitis). The physiological consequences of these progressive changes are the reduction in lung elastic recoil, airflow limitation (that is not fully reversible), air trapping, and hyperinflation.[7] The air trapping and hyperinflation observed in patients with emphysema-predominant disease result in increased total lung capacity and residual volume,[7] whereas the airflow limitation leads to the reduction of forced expiratory flow in 1 s (FEV1). The clinical translation of the physiological changes is a progressive reduction in exercise capacity and quality of life.[7]

The treatment strategies in COPD have been moving from a "one-size-fits-all" approach in the past toward more personalized medicine.[8] The current treatment approaches are multimodal and encompass smoking

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cessation, vaccinations against common pathogens causing pneumonia, inhaled pharmacological therapies, and pulmonary rehabilitation.[9] Long-term home oxygen therapy, domiciliary noninvasive ventilation, and lung transplantation are therapeutic options in selected patient groups.[9] The treatment of COPD aims to reduce morbidity and mortality and improve quality of life.[9] Prognostically, it is well-established that the degree of static lung hyperinflation is an independent predictor of poor prognosis in patients with COPD, irrespective of the BODE index.[10] In patients with emphysema-predominant disease, lung volume reduction surgery (LVRS) may offer clinical and prognostic benefits.[11,12] LVRS aims to reduce hyperinflation in patients with emphysema, thereby reshaping the diaphragm which may lead to the improvement in breathing mechanics.[12] It also works by sacrificing parts of the lungs with severe disease and allowing for better ventilation of remaining parts of the lungs that are less affected by the disease.[12] LVRS may improve lung function parameters, exercise capacity, quality of life, and prognosis, particularly in those who have both predominantly upper-lobe emphysema and low baseline exercise capacity.[11,12] Nevertheless, there is a significant associated risk of adverse events and mortality.[12]

More recently, a number of minimally invasive bronchoscopic lung volume reduction (BLVR) techniques have been developed, and these techniques may offer clinical benefits in those who are unfit for LVRS as alternative options. Bronchoscopic valves achieve lung volume reduction by lobar collapse through regulating lobar airflow, while lung volume reduction coils (LVRCs) and bronchoscopic thermal vapor ablation act principally by inducing tissue compression mechanically or through inflammatory processes. Another BLVR technique that has been explored is biological lung volume reduction using a sealant. In this up-to-date review, we will discuss the clinical implications, risks of complications, and gaps in knowledge in BLVR techniques.

ENDOBRONCHIAL VALVES

Clinical efficacy

Endobronchial valves (EBVs, Zephyr®, PulmonX Corp., Redwood City, CA, USA) are one-way valves that are implantable during bronchoscopic procedures which prevent air from entering a selected lobar bronchus, induce atelectasis of the chosen segment of the lung, and thereby achieve lung volume reduction [Figure 1].

The first randomized controlled trial (RCT) comparing EBV to standard medical care in patients with advanced emphysema demonstrated an overall modest improvement in the lung function and 6-min walk distance (6MWD).[13] The subgroup of patients with high heterogeneity on computer tomography (CT) with upper lobe-predominant emphysema and complete fissure had a better response

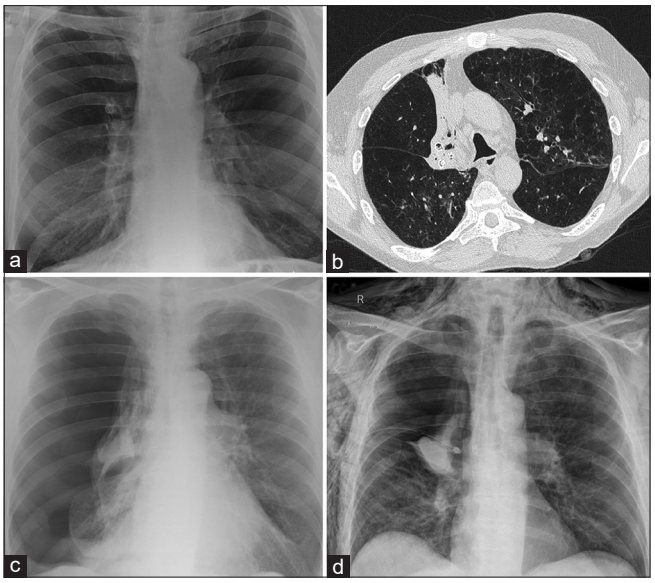

Figure 1: (a) Pulmonx endobronchial valves (EBV) inserted in the right upper lobe (RUL); (b) RUL atelectasis after EBV; (c) right tension pneumothorax 48 h after EBV procedure; (d) right chest drain inserted with significant surgical emphysema

to treatment at 6- and 12-month follow-up in the *post hoc* analysis.[13] As a result, in the subsequent RCTs, the emphysema distribution and fissure integrity were readily assessed during patient selection. While most EBV trials recruited patients with heterogeneous emphysema only,[14-16] Klooster *et al*. and Herth *et al*. recruited patients with both homogeneous and heterogeneous emphysema.[17,18] Although homogeneous distribution does not preclude achieving lung volume reduction and good clinical outcome in EBV-treated patients, it is clear that patients with heterogeneous emphysema respond better.[13-18] The IMPACT trial further confirmed the clinical efficacy of EBV in homogeneous emphysema[19] [Table 1].

Complications

Pneumothorax has been recognized consistently as a common and important adverse event in EBV-treated patients. The prevalence of pneumothorax post-EBV implantation varies from 4.2% to 29.2%, with a higher prevalence in the later trials.[13-19] The occurrence of pneumothorax is thought to be due to the rapid shifts in lung volumes as a result of lobar collapse, the rupture of existing blebs/bullae, or rupture of lung parenchyma due to preexisting adhesions.[19,27] The increased risks of pneumothorax in the later trials may be due to better patient selection and hence more complete and rapid atelectasis of selected lung segments. The onset of pneumothorax typically occurs within the first 2 days after the procedure but can often take place beyond this point.[27,28] This marks the importance of short inpatient stay and the need for close observation during this period.

Other common adverse events in EBV-treated patients include COPD exacerbations, pneumonia, and valve

Table 1: Clinical outcome of bronchoscopic lung volume reduction techniques in randomized controlled trials at 6 and 12 months

RCT	Heterogeneous emphysema (%)*	Percentage of FCα	Controlled group	Between-group differences at 6 months**					Between-group differences at 12 months**					Pneumothorax (%)
				Percentage reached MCID (treatment vs. control)	FEV1 (ml)	RV (ml)	6MWD (m)	SGRQ	Percentage reached MICD (treatment vs. control)	FEV1 (ml)	RV (ml)	6MWD	SGRQ	
Endobronchial valves														
Sciurba *et al.*, 2010[13]	51	38	SMC	FEV_1 (>15% improvement): 24% versus 11% BODE (1 point improvement) 40% versus 19%	+60.0	NS	+19.1	−3.4	FEV_1 (>15% improvement): 29% versus 5%	65.3	n/p	11.7	-	4.2
Kemp *et al.*, 2017[15]	100β	100	SMC	FEV1 (≥12% improvement): 56% versus 3% RV (≥430 ml reduction) 58% versus 26% 6MWD (≥26 m improvement): 52% versus 13% SGRQ (≥4-point reduction): 62% versus 34% mMRC (≥1 point reduction): 44% versus 23%	+230	−670	+79	−6.5	-	-	-	-	-	29.2
Criner *et al.*, 2018[16]	100	100	SMC	-	-	-	-	-	FEV_1 (≥15% improvement): 48% versus 17%	106	−522	+39	−7.1	26.6
Klooster *et al.*, 2015[17]	47	100	SMC	FEV_1 (>10% improvement): 72% versus 24% RV (>430 ml reduction): 71% versus 3% SGRQ (>4-point reduction): 79% versus 33% 6MWD (≥26 m improvement): 87% versus 6% RV/TLC (>4% reduction): 63% versus 9% Clinical COPD Questionnaire score (>0.4-point reduction): 63% versus 27%	+191	−831	+106	−14.7	-	-	-	-	-	18.0
Herth *et al.*, 2012[18]	n/p	40	SMC	n/p	+14%Ŧ	n/p	NS	−9Ŧ	n/p	15%Ŧ	-	NS	NS	8.1
Intrabronchial valves														
Wood *et al.*, 2014[20]	n/p	n/p	Sham	NS	−70	+380	−20.6	+3.6	-	-	-	-	-	2.1
Li *et al.*, 2019[21]	100	100	SMC	FEV_1 (≥15% improvement): 41% versus 21%	+115	NS	+36.4	−10.5	-	-	-	-	-	7.6

Contd...

Table 1: Contd...

RCT	Heterogeneous emphysema (%)*	Percentage of FCα	Controlled group	Between-group differences at 6 months**					Between-group differences at 12 months**					Pneumothorax (%)
				Percentage reached MCID (treatment vs. control)	FEV1 (ml)	RV (ml)	6MWD (m)	SGRQ	Percentage reached MICD (treatment vs. control)	FEV1 (ml)	RV (ml)	6MWD	SGRQ	
Criner *et al.*, 2019[22]	100	100	SMC	FEV_1 (≥15% improvement): 37% versus 10% RV (≥310ml reduction): 51% versus 32% mMRC (≥1 point reduction): 53% versus 18% SGRQ (≥ 4-point reduction): 54% versus 18% 6MWD (≥25 m improvement): 32% versus 23%	+101	−361	+6.9	−13	FEV_1 (≥15% improvement): 37% vs.5% mMRC (≥1 point reduction):49% vs 7% SGRQ (≥ 4-point reduction): 51% vs. 22%	99	-	-	−9.5	28.3
Lung volume reduction coils														
Sciurba *et al.*, 2016[23]	23	n/a	SMC	-	-	-	-	-	6MWD (≥25m improvement): 40% vs. 27% SGRQ (≥4-point reduction): 61% vs. 28%	+7%[Ŧ]	−310	+14.6	−8.9	9.7
Deslée *et al.*, 2016[24]	n/p	n/a	SMC	6MWD (≥54 m improvement): 36% versus 8%	+90	−370	+21	−13.4		+80	−360	NS	−10.6	6.0 as serious adverse events
Bronchoscopic thermal vapor ablation														
Herth *et al.*, 2016[25]	100 (upper lobe predominant)	22	SMC	FEV_1 (≥12% improvement): 50% versus 13% SGRQ (≥8-point reduction): 53% versus 17 6MWD (≥26 m improvement): 42% versus 23%	131	−303	-	−9.7	-	-	-	-	−12.1	2
Shah *et al.*[26]	100 (upper lobe predominant)	0	SMC	-	89	−306	NS	NS	-	112	-	-	−8.4	

*Percentage calculated within the treatment group, [α]Defined as at least 90% intact fissure visible on CT, [β]Defined as ≥10% heterogeneity, **Only statistically significant data are presented, [∞]Presented results from overall analysis in each trial. Subgroup analysis demonstrates better outcome, [Ŧ]Data presented in percentage change from baseline between groups in patients with complete fissures only. NS: Nonsignificant, n/p: Not presented in the published articles , SMC: Standard medical care, FC: Fissure completeness, MCID: Minimum clinical important difference, FEV1: Forced expiratory volume in 1 s, RV: Residual volume, TLC: Total lung capacity, 6MWD: 6-min walk distance, SGRQ: St. George Respiratory Questionnaire, RCT: Randomized controlled trial

migration in the published studies.[13-19] The reported mortality rate was 0.9%–8.0% in patients with end-stage COPD at 6- to 12-month follow-up.[13-19]

Long-term benefit

Despite several RCTs demonstrating the significant clinical benefit of EBV in COPD, the long-term efficacy remains unclear beyond 12 months. Venuta *et al*. prospectively studied longitudinal survival benefit in 40 patients who underwent EBV.[29] In this study, patients with and without visible fissures were included, and the survival benefit in those who had complete fissure was significantly better compared to those without at 5 years (83% vs. 24%). More recently, Gompelmann *et al*. retrospectively investigated the durability of the benefit of EBV in 256 patients.[30] In this study, only patients who had the absence of collateral ventilation (CV) were included in the analysis. Due to losses to follow-up and death, only half of patients completed a 1-year assessment and a quarter at 3 years. Despite clinical benefit sustained within the 1st year, the marked decline is notable beyond this point, and only a few parameters remained statistically significant compared to baseline 3 years later.[30] Although the decline may be due to the natural progression of the COPD, comparison with matched controls in a prospective study is imperative before conclusions can be drawn.[30] Strikingly, despite stringent patient selection, up to 25% of patients required permanent removal of all valves during the first 3 years, of which more than half were due to the lack of clinical benefit.[30] In 449 patients who were treated with EBV, a better survival benefit was observed in patients who achieved valve-induced lobar atelectasis compared to the rest of patients at follow-up for up to 5 years.[31] A 10-year follow-up of 19 EBV-treated patients also confirmed this.[32] However, complete lobar atelectasis was only achieved in less than a third of patients in both studies (26%–29%), and there were some disparities in baseline characteristics between groups which may account for the differing in survival rates.[31,32]

While the variations in achieving valve-induced lobar atelectasis may be operator dependent, in study settings, high standard, effective procedures are often delivered by experienced intervention pulmonologists in specialist centers. Even among CV-negative patients, treatment response and the long-term benefit of EBV remain heterogeneous,[32] suggesting that other factors may influence treatment efficacy and disease outcome. Clearly, larger prospective and randomized studies are crucial in determining the predictors for long-term clinical benefit and survival in EBV-treated patients.

Assessment of collateral ventilation

The absence of CV between the target lobe and adjacent lobes, through means of fissure completeness, is the key feature for predicting better outcome in patients receiving bronchoscopic valves.[13-19] Therefore, using radiological and endoscopic techniques to assess fissure integrity is of vital importance at the patient selection stage of the treatment. CT fissure analysis and Chartis™ Pulmonary Assessment System are the two common methods used.

Chartis™ Assessment System is a medical device consisting of a single-use catheter with a compliant balloon component at the distal tip, which inflates and seals the airway during bronchoscopy before the placement of EBVs.[33] The air within the target lobe can flow out only through the Chartis catheter lumen, while no air will flow in. The airflow and pressure are measured and displayed on a Chartis console. In a target lobe without CV, the airway flow would gradually stop after inflation of the balloon and the airway resistance would increase, whereas in a target lobe with CV, the airflow would be persistent.[33] Chartis™ was a safe and effective method in assessing CV with 90% accuracy in predicting post-EBV atelectasis in 20 prospectively recruited patients in the feasibility study.[34] A subsequent larger study by Herth *et al*. demonstrated that Chartis had 75% accuracy in predicting reduction of total lung volume (by >350 ml) after EBV implantation if used alone.[35] Gompelmann *et al*. confirmed that Chartis had a positive predictive value of above 70% and a negative predictive value of 80% in a retrospective analysis.[36] As the accuracy of Chartis measurement may be impeded by coughing, multiple mucus plugging, or inexperienced operators, adequate training is mandatory to maximize the success and reliability of the assessment.[37]

Qualitative CT fissure analysis is a noninvasive alternative and an indirect measurement of interlobar CV by studying fissure integrity. If this is performed by experienced radiologists, interobserver discrepancies are minimal.[38,39] Several retrospective studies assessing the accuracy of CT determination of fissure completeness or near completeness demonstrated comparable accuracy in identifying responders when compared with Chartis.[36,40] However, CT and Chartis classification of CV have a 27%–33% discordance rate.[34,40,41] Fiorelli *et al*.[42] reviewed 12 studies comparing CT and Chartis™ methods in predicting clinical response to EBV. The authors suggested that in those with >95% fissure completeness on CT, further Chartis assessment adds little value but results in additional costs, while a fissure integrity of <75% on CT predicts failure in achieving lobar atelectasis in 100% of patients. In individuals with CT fissure integrity of between 75% and 90%, additional Chartis assessment before valve implantation could provide additional value in patient selection.[42]

Intrabronchial valves

Intrabronchial valves (IBVs, Spiration®, Redmond, WA, USA) have a similar mechanism of action to EBV but differ in shape and structure. The early pilot study in IBV demonstrated an improvement in health-related quality of life.[43] The subsequent randomized sham-controlled trials aimed to investigate the clinical efficacies of partial lobar occlusion in upper lobe-predominant emphysema. Although the incidence of pneumothoraces was lower than many other bronchoscopic valve RCTs (2.1%–7.6%),

the outcome failed to reach clinical meaningful endpoints at 3- and 6-month follow-up.[20,44] More recently, both REACH and EMPROVE trials assessed the clinical efficacy of IBV in patients with severe heterogeneous emphysema and confirmed interlobar fissure integrity by complete lobar occlusion.[21,22] With better patient selection and better methodology, both RCTs have demonstrated a statistically significant improvement in lung function parameters, exercise capacity, and quality of life with IBV at 3/6- and 6/12-month follow-up [Table 1].

LUNG VOLUME REDUCTION COILS

Principal mechanisms

LVRCs (PneumRx, Inc.) are implantable devices that aim to reduce lung volume by mechanically compressing the emphysematous lung parenchyma. Unlike EBV, the coils are nonblocking and composed of nitinol, a nickel–titanium metal alloy with memory-shaped and superelastic properties. They are placed in the subsegmental bronchi of the most emphysematous lobe that has previously been identified using high-resolution CT. The coils are inserted bronchoscopically in their straight form and return to their default coil shape once deployed[45] [Figure 2]. Fluoroscopy is used for real-time visualization of the coil to guide insertion. It is proposed that the mechanism underlying the benefits of coil treatment includes the conformational change that precipitates the retraction of the surrounding diseased lung parenchyma and allowing more space for healthier lung portions to expand.[45] As air cannot progress beyond the coil, it is redirected to more functional lung parts. The compression of the lung tissue also augments the lung elastic recoil and tethers open small airways nearby, preventing their collapse on expiration.[45] These factors collaboratively reduce gas trapping and hyperinflation and improve pulmonary function.[45,46] The advantage of LVRC over EBV is its independence of interlobar CV and effectiveness in both heterogeneous and homogeneous emphysema.[23,45-49]

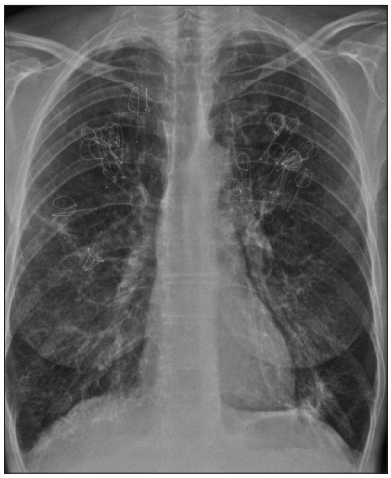

Figure 2: Bilateral upper-lobe lung volume reduction coils in a patient with severe emphysema and significant hyperinflation

Short- and long-term efficacy

Following the initial pilot studies which confirmed the feasibility of LVRC,[45-48] three RCTs were subsequently conducted.[23,24,49] The RESET trial included 47 patients with heterogeneous and homogeneous emphysema and demonstrated a significant improvement in lung function parameters, quality of life, and 6MWD in LVRC-treated patients at 90 days postprocedure compared to standard of care.[49] Further uncontrolled follow-up of all the patients at 180 and 360 days postprocedure demonstrated that statistical significance of the improvement was maintained at 360 days from baseline; however, the magnitude of benefit gradually declines over time.[50] The subsequent RCTs (RENEW and REVOLENS trials) with long-term follow-up confirmed the clinical benefit in the LVRC group over standard medical care at 6 and 12 months[23,24] [Table 1]. Once again, a reduced improvement in exercise capacity in LVRC-treated patients at 12 months was reported in the REVLONS trial.[24] At 2-year follow-up, only St George's Respiratory Questionnaire (SGRQ) scores and RV remained statistically significantly improved compared to baseline, and the small improvement in RV (by 280ml) may be less clinically important.[51] Hartman *et al*. retrospectively evaluated the long-term outcome of 38 patients after LVRC treatment at 1, 2, and 3 years.[52] A decline in clinical benefits was also observed over the 3-year follow-up. However, it is unclear if such decline in clinical benefit is due to the natural disease progression.

A significant proportion of LVRC-treated patients in the clinical trials did not reach the endpoint of minimally clinically important difference (MCID)[23,24,49] in the responder analysis, and the predictors of outcome remain unclear to date. Deslee *et al*. performed a multivariate analysis in a multicenter prospective cohort study to evaluate the relationship between the type of emphysema, degree of hyperinflation, and treatment outcome. After 6-month follow-up, none of the variables appear to be meaningful predictors.[51] In the RESET trial, there was no significant difference in outcome between the homogeneous and heterogeneous emphysema groups.[49] Slebos *et al*. found that the number of coils inserted also did not affect the clinical outcome. However, a higher RV was an independent predictor for better outcome.[53] The RENEW trial showed that the subgroup with RV ≥225% predicted and heterogeneous emphysema yielded a greater magnitude of improvement in median FEV1, RV, 6MWD, and mean SGRQ compared to the group with RV <225% predicted and homogeneous emphysema.[23] In addition, the presence of four or more comorbidities or cardiac-related comorbidity reduced the 6MWD outcome despite the improvement in lung function compared to the control group at 12 months.[23] The ongoing ELEVATE trial (NCT03360396) is a multicenter prospective RCT to confirm the previous RCT findings, and the results of this trial may further elucidate favorable selection criteria for LVRC treatment.

To date, there is no head-to-head randomized control trial comparing LVRC against other lung volume reduction

modalities. Marchetti *et al*. retrospectively compared LVRC with LVRS and standard medical therapy in patients with advanced homogeneous emphysema.[54] Better lung function and exercise capacity were observed in patients with LVRC compared to those who received medical therapy, and significantly better survival was achieved in both LVRC and medical therapy groups compared to LVRS at 12 months.

Health economics

The cost-effectiveness analysis in REVOLENS trial at 1 year demonstrated a high short-term cost. The incremental cost-effectiveness ratio (ICER) was estimated at $782,598 per additional quality-adjusted life-year (QALY) with only moderate clinical benefit.[24] At 2 years, the ICER was estimated at €75,978 per QALY and treating patients early was significantly more expensive but also more effective.[55] In this context, further follow-up is needed to evaluate the long-term impact of LVRC treatment on the health economics in patients with severe emphysema.

Bronchoscopic thermal vapor ablation

Bronchoscopic thermal vapor ablation (BTVA, InterVapor®; Uptake Medical Technology, Seattle, WA, USA) is a newer modality of BLVR technique using steam. Heated water vapor is delivered through a specialized balloon catheter to a targeted lung region using a bronchoscope.[55] The heated water vapor induces a local inflammatory response, thereby causing local atelectasis and fibrosis over a few weeks to months.[56,57] The steam ablation treatment is performed in a staged manner [Figure 3]. This technique is a treatment option for heterogeneous upper lobe-predominant emphysema and is independent of CV. One of the advantages of BTVA over EBV and LVRC is that this BLVR technique does not involve implantation of metalwork within the lungs.

The STEP-UP trial evaluated the safety and efficacy of BTVA in patients with upper lobe-predominant emphysema and compared it with standard medical care.[25] This study demonstrated a significant improvement in lung function and quality of life in the BTVA-treated group compared to the control at 6 months. Approximately two-third of the intervention arm reached MCID [Table 1]. However, between-group differences in 6MWD failed to reach statistical significance. The 12-month follow-up showed significant but slightly reduced between-group difference in FEV1 and a sustained improvement in SGRQ.[26]

Common adverse events of BTVA were COPD exacerbations (9%–24%) and pneumonia (18%–23%).[25,58] However, the increased localized inflammatory response to BTVA and clinical manifestations of respiratory symptoms within 30 days postprocedure are positive predictors of better long-term outcome.[58] The risk of pneumothorax was low (2%–3%) compared to EBV, IBV, and LVRC.[25] This is likely to be due to less rapid reduction in lung volumes in BTVA-treated patients compared to EBV and LVRC, as this typically occurs over several weeks to months.[58]

Lung sealant and biological lung volume reduction

AeriSeal emphysematous lung sealant (Aeris Therapeutics, Inc., Woburn, MA, USA) is another nonblocking BLVR technique. The sealant is composed of aminated polyvinyl alcohol (4.5 mL, 2.1% w/v) and glutaraldehyde (0.5 mL,

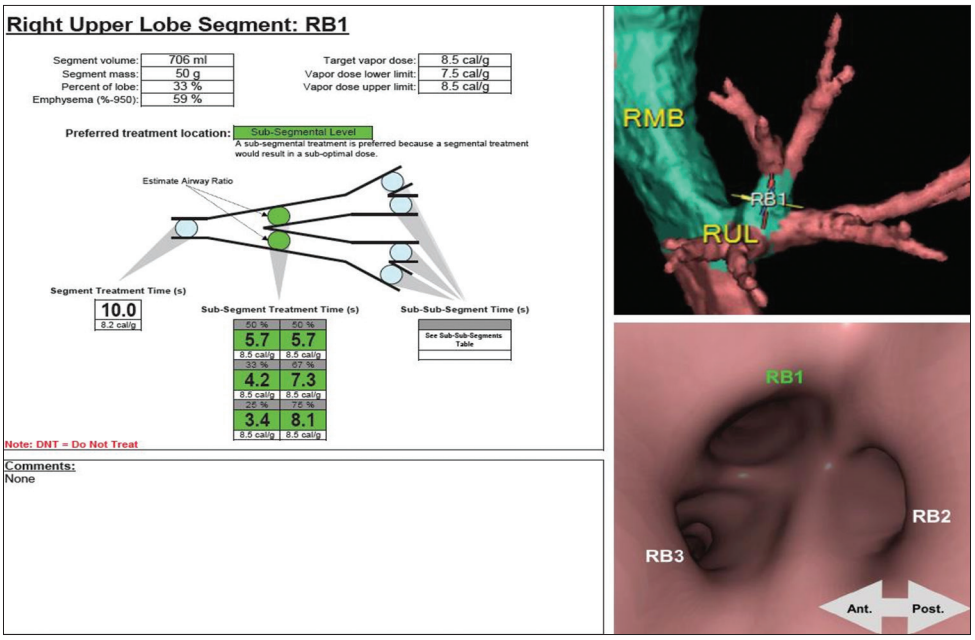

Figure 3: A dedicated software – the InterVapor Personalized Procedure Program (IP3) is used for treatment planning in bronchoscopic thermal vapor ablation procedure (Courtesy of Uptake Medical Corporation, Seattle, USA). In this patient, the preferred site of treatment is subsegment of right upper lobe (RB1) and the target vapor dose is 8.5Cal/g and the treatment time is 10 s

1.25% w/v).[59] These two compounds are mixed with air to form a foam and then delivered immediately using a dedicated catheter through a bronchoscope to the desired segments. It closes off small airways and alveoli and also induces local airway inflammation followed by fibrotic process which results in lung volume reduction.[59] Despite the demonstration of some initial clinical efficacy,[60] the ASPIRE RCT was terminated early due to unacceptable adverse events.[61]

Injection of low-cost biological agents such as autologous blood and fibrin glue containing fibrinogen and thrombin is a novel BLVR approach which achieves lobar atelectasis by inducing airspace inflammation, remodeling, and scarring.[62] Bakeer *et al*. used either agent in 15 patients with severe heterogeneous emphysema.[63] This pilot study demonstrated satisfactory safety and significant improvement in 6MWD, SGRQ, lung function parameters, and radiological lung volume reduction at 12 months postprocedure compared to baseline in both groups.[63] The ongoing BLOOD-VALVES trial (NCT03010449) will assess clinical efficacy when a combination of autologous blood and IBV is used in heterogeneous emphysema.

Other emerging bronchoscopic techniques

A number of emerging bronchoscopic techniques are being evaluated in clinical trials. These techniques are technically not aimed at reducing the lung volumes and therefore may potentially apply to wider phenotypes of patients with COPD. The RejuvenAir system (CSA Medical, Lexington, MA, USA) is a CE-marked medical device which utilizes liquid nitrogen which is delivered as metered cryospray (−196C°) through the bronchoscope to destroy airway surface and induce healing. This technique is being developed as a treatment for chronic bronchitis. Preliminary data in 35 patients have demonstrated a satisfactory safety profile and significant improvement in SGRQ and 6MWD.[64] The ongoing large RCT (NCT03893370) will provide more insight into clinical efficacy. Bronchial rhinoplasty (RheOx™, Gala Therapeutics, USA) uses pulsed electric fields to ablate the mucous-producing airway epithelial cells. It was found to have a favorable safety profile

Table 2: Summary of patient selection criteria - best practice recommendations from expert panels

	EBV[69]	LVRC[70]	BTVA[71]
Spirometry and hyperinflation*			
FEV_1	15%-50% predicted	≤45% predicted	20-45% predicted
RV	>175% predicted	>200% predicted or 175%-200% if RV/TLC ≥0.58	≥175% predicted
TLC	>100% predicted	-	-
DLCO	-	-	≥20% predicted
Symptoms and exercise performance			
mMRC		>1	≥2
6MWD	100-500 m If <200 m, reassessment after pulmonary rehabilitation	140-450 m	140-500 m
Emphysema morphology** and distribution			
Heterogeneity*	Heterogeneity preferred, but homogeneous emphysema is not an exclusion criterion	Heterogeneous and homogeneous	Upper lobe-predominant emphysema with low disease severity of lower lobe
Centrilobular	-	Suitable	-
Moderate panlobular	-	Suitable	-
Severe panlobular	-	Not suitable	-
Giant bullae	-	Not suitable	-
Paraseptal	-	Not suitable	-
Lobular destruction	-	Potential site of treatment: 20%-80% at the −950 HU threshold on a low (or "soft") kernel reconstructed thin-slice (1 mm) high-resolution CT	-
Fissure integrity∞	>95% Or 80%-95% and Chartis confirmation	Not necessary	Not necessary
Contraindications	Severe hypercapnia (>60 mmHg on room air) (to be reconsidered after 3 months of noninvasive ventilation) Severe hypoxemia (<45 mmHg on room air) Evidence of significant coexistent pulmonary pathology on HRCT Current smoker Unstable COPD	Frequent cough Severe bronchial hyperresponsiveness Sputum production Frequent exacerbation	Severe hypoxemia (<50 mmHg on room air) Hypercapnia (≥50 mmHg on room air) Left ventricular ejection fraction <40% Severe pulmonary hypertension Unstable COPD

*No clear definition but generally defined as a >25% difference in the proportion of pixels of < −910 HU or a >15% difference in the proportion of pixels of < −950 HU between the targeted lobe and the ipsilateral adjacent nontargeted lobe. HUs: Hounsfield units, EBV: Endobronchial valve, LVRC: Lung volume reduction coils, BTVA: Bronchoscopic thermal vapor ablation, FEV_1: Forced expiratory volume within 1 s, RV: Residual volume, TLC: Total lung capacity, 6MWD: 6 min walk distance, mMRC: Modified Medical Research Council, CT: Computed tomography, COPD: Chronic obstructive pulmonary disease, HRCT: High-resolution CT, DLCO: diffusing capacity for carbon monoxide, *Measured by body plethysmography, **Measured by HRCT, ∞Measured by quantitative CT

and provided symptom improvement and quality of life at 6- and 12-month follow-up in 31 patients with chronic bronchitis in the pilot study.[65] Targeted lung denervation (TLD) (Holaira, Minneapolis, MN, USA) involves radiofrequency ablation of the parasympathetic innervation of airways and thereby leads to the reduction of bronchoconstriction and viral/inflammation-induced airway hyperresponsiveness.[66-68] Recently, the AIRFLOW-2 trial has demonstrated that patients who received TLD had significantly lower respiratory adverse event and hospitalization compared to sham-controlled group within the 1st year.[67] Future larger scaled studies are warranted to confirm its clinical efficacy.

DISCUSSION

With the increasing advances in bronchoscopic techniques, treating patients with severe emphysema/COPD requires a multidisciplinary approach involving expert input from pulmonologists, chest radiologists, and thoracic surgeons. The development of these techniques is recent, and they are not yet widely available. It is preferable that only specialist centers with trained and experienced interventional pulmonologists provide BLVR treatment, ideally in the form of a registry or within the context of further prospective studies.

Correct patient selection is imperative for optimal clinical outcome[69-71] [Table 2]. The baseline characteristics of recruited patients in clinical trials provide guidance on patient selection in clinical practice [Table 3]. For instance, patients with FEV1 of 20%–45% predicted, RV of >200%, 6MWD of >140 m, and Modified Medical Research Council Dyspnea Scale of at least 2 are likely to respond to treatment. On the contrary, individuals with baseline characteristics that are well outside these reference values, who are current smokers, and those who are not on maximal medical therapy and have not completed pulmonary rehabilitation are less likely to respond to BLVR treatment and may not be suitable candidates.

While the effect of EBV/IBV is reversible by removing the valve, LVRC is only considered to be partially reversible.[67] The effect of other bronchoscopic techniques such as BTVA, TLD, RejuvenAir system, and bronchial rheoplasty is irreversible. These factors should be carefully considered and communicated to patients during procedure planning. Although it is relatively well-established that heterogeneity and absence of CV are the key predictors for better outcomes in EBV/IBV, the predictors for optimal response are less clear for other techniques.

The Cochrane meta-analysis on BLVR in 2017 confirms that EBV and LVRC procedures can provide significant

Table 3: The baseline characteristics of included participants in randomized controlled trial

RCT	Number (*n*)*	Number of months for endpoint assessment	Emphysema distribution	Baseline FEV_1 (% predicted)	Baseline RV (% predicted)	Age (years)	mMRC	6MWD (m)
Endobronchial valves								
Sciurba *et al*., 2010[13]	220	6, 12	Homogeneous and heterogeneous	30±8	216±44	65±7	n/p	334±87
Davey *et al*., 2015[14]	25	3	Heterogeneous	32±10	219±39	62±7	4±1∞	342±94
Kemp *et al*., 2017[15]	65	3, 6	Heterogeneous	30±9	249±52	65±8	3.0±0.8	282±94
Criner *et al*., 2018[16]	128	12	Heterogeneous	28±7	225±42	64±7	2.4±1	311±81
Klooster *et al*., 2015[17]	34	6	Homogeneous and heterogeneous	29±7	216±36	58±10	2.7±0.8	372±90
Herth *et al*., 2012[18]	111	6, 12	Homogeneous and heterogeneous	29±8	240±51	60±8	n/p	341±108
Valipour *et al*., 2016[19]	43	3	Homogeneous	28±6	277±55	64±6	2.7±0.8	308±91
Intrabronchial valve								
Ninane *et al*., 2012[44]β	37	3	Upper lobe predominant	35±10	238±74	61±7	2.8±0.7	337±106
Wood *et al*., 2014[20]β	142	6	Upper lobe predominant	30±8	216±50	65±6	2.7±0.7	314±89
Li *et al*., 2019[21]	66	3, 6	Heterogeneous	27±7	261±74	64±7	2.7±0.6	339±95
Criner *et al*., 2019[22]	113	6, 12	Heterogeneous	31±8	208±45	67±7	2.7±0.7	304±85
Lung volume reduction coils								
Sciurba *et al*., 2016[23]	158	12	Homogeneous and heterogeneous	26±6	246±39	63±8	3 (2-4)Ŧ	312±79
Deslée *et al*., 2016[24]	50	6, 12	Homogeneous and heterogeneous	26±8	271±38	62±8	3 (2-4)Ŧ	300±112
Zoumot *et al*., 2015[50]	45	12	Homogeneous and heterogeneous	28±8	225±50	64±8	2 (1-4)Ŧ	310±32
Bronchoscopic thermal vapor ablation								
Herth *et al*., 2016[25]	45	3, 6	Heterogeneous (upper lobe predominant)	33±8%	235.0±40.3%	64 (46-74)**	n/p	356±92

Data expressed in mean±SD. *Number randomized to intervention group, ∞MRC, **Median (IQR), ŦPresented as median (range), *Measured by body plethysmography, **Measured by HRCT, ∞Measured by quantitative CT, βNegative clinical trials. IQR: Interquartile range, n/p: Not presented, SD: Standard deviation, MRC: Medical Research Council, RCT: Randomized controlled trial, FEV_1: Forced expiratory volume within 1 s, RV: Residual volume, 6MWD: 6 min walk distance, mMRC: Modified MRC

and clinically meaningful improvements in lung function, quality of life, and exercise tolerance up to 12 months in highly selected group of patients. However, existing data only represent the short-term outcome.[72] The lack of reliable long-term outcome data suggests that the survival benefit, the durability of the clinical benefit, and long-term cost-effectiveness remain unclear.[72] Most BLVR trials were designed to compare with standard medical care, which may have led to a significant risk of bias, particularly when the endpoint of the trials included unblinded measurements of patient-reported quality of life. The only sham-controlled trial of EBV conducted by Davey *et al.* assessed clinical efficacy at 3 months, and therefore, the long-term efficacy compared to sham-controlled arm beyond this is unknown.[14]

Although the established BLVR techniques may offer options to different subgroups of severe emphysema population, there is also a significant overlap of patients who would be eligible for more than one type of BLVR therapy.[73] To date, there is no head-to-head trial comparing these BLVR treatments, making it challenging to decide which BLVR technique is superior in such overlapping patient groups. The ongoing observational registries in the UK and the Netherlands (ISRCTN16371361 and NCT02815683) are prospective postmarketing studies with long-term follow-up outcomes of patients who are treated with BLVR procedures. These studies will hopefully provide guidance in such clinical situations.

CONCLUSION

Advances in bronchoscopic intervention potentially allow a personalized approach in managing selected patients with severe emphysema and chronic bronchitis. Short-term clinical efficacy has been demonstrated in randomized clinical trials, with some of the bronchoscopic techniques available and discussed above. Further research is needed to establish long-term clinical benefits, durability, and cost-effectiveness.

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Conflicts of interest
There are no conflicts of interest.

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