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REVIEW

Which Endoscopic Procedure to Use and in What Patient? Valves, Coils, Foam, and Heat in COPD and Asthma

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ABSTRACT

Despite the latest developments in therapeutic agents targeting airway endotypes, a significant proportion of patients with asthma and chronic obstructive pulmonary disease (COPD) remain symptomatic. Endoscopic therapies have a complementary role in the management of these airway diseases. The sustained efficacy of bronchial thermoplasty (BT) among patients with asthma over 10 years has been encouraging, as it has been shown to improve symptom control and reduce hospital admissions and exacerbations. Studies suggest that BT helps ameliorate airway inflammation and reduce airway smooth muscle thickness. While studies suggest that it is as effective as biologic agents, its role in the management of severe asthma has yet to be clearly defined and GINA 2022 still suggests limiting its use to patients with characteristics of the various populations studied. Conversely, bronchoscopic lung volume reduction has shown promise among patients with advanced COPD. Rigorous patient selection is important. Patients with minimal collateral ventilation (CV) and higher heterogeneity index have shown to benefit the most from endobronchial valve (EBV) therapy. For those with ongoing CV, endobronchial coils would be more appropriate. Both therapeutic modalities have demonstrated improved quality of life, effort tolerance, and lung function indices among appropriately selected patients. The emerging evidence suggests that endoscopic procedures among airway disease still have a substantial role to play despite the development of new therapeutic options.

Keywords: Obstructive airway disease; Asthma; Bronchothermoplasty; COPD; Lung volume reduction; Endobronchial valve; Endobronchial coil

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Key Summary Points

Bronchial thermoplasty is effective in reducing hospital admissions and improving symptom control up to 10 years.

Bronchial thermoplasty appears effective among patients with asthma with both eosinophilic and non-allergic endotypes.

Among carefully selected patients with COPD with heterogeneous emphysematous patterns and minimal collateral ventilation, endobronchial valves are effective in improving lung function indices, exercise tolerance, and quality of life.

Endobronchial coils is an alternative endoscopic therapy among patients with COPD regardless of collateral ventilation status.

Other endoscopic therapies for patients with COPD are still in the pilot stages of evaluation and are not meant for routine practice in the current state.

INTRODUCTION

Over the past two decades, the prevalence rates of asthma and chronic obstructive pulmonary disease (COPD) have risen significantly, taking positions in the top 20 chronic diseases in 2019 [1–3]. Health-care resource utilization in the USA has increased considerably, with projected costs of US$963.5 billion and US$800.9 billion for asthma and COPD, respectively, over 20 years [4, 5]. As precision medicine takes center stage, there is enhanced appreciation of the need to characterize and target therapies according to airway endotypes [6, 7]. About 5–10% of asthmatic sufferers remain symptomatic despite interventions directed at optimizing pharmacotherapeutics, allergen control, smoking cessation, and management of comorbidities [8]. The Global Initiative for Asthma (GINA) recommends biologic agents and/or bronchial thermoplasty (BT) for patients with severe asthma [9]. With the proliferation of biomarker-driven therapies [10], BT is recommended under clinical trial settings or registries that track BT long-term safety and effectiveness. Current evidence for BT suggests a complementary role for patients with severe asthma [11–13]

Medical management of COPD includes short and long-acting bronchodilators, inhaled corticosteroids, oxygen supplementation, pulmonary rehabilitation, and smoking cessation therapy. In advanced emphysema with significant hyperinflation, patients continue to experience dyspnea and exacerbations where pharmacological interventions have limited benefit [14–19]. The National Emphysema Treatment Trial (NETT) explored lung volume reduction surgery (LVRS) as a treatment modality and demonstrated survival benefit, improved quality of life, and exercise tolerance in those with upper lobe emphysema and low baseline exercise capacity [20]. However LVRS is associated with high morbidity associated with persistent air leak and prolonged hospitalization with significant early postoperative mortality rate of 10% [21, 22]. This has led investigators to find novel ways to perform LVR via bronchoscopy (BLVR) [18].

We review different endoscopic techniques for COPD and asthma and how patient selection is key to favorable outcome. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

ASTHMA AND BRONCHIAL THERMOPLASTY

Bronchial thermoplasty (BT) is an endoscopic procedure where radiofrequency energy is applied via a catheter. Radiofrequency energy is converted to heat at 65 °C for 10 s to target airways between 3 and 10 mm in diameter [23–25]. BT is performed under general anesthesia or moderate sedation, starting with the

Table 1 Landmark papers for bronchial thermoplasty

Landmark papers	Study population	Number of subjects	Follow-up	Outcomes	Adverse events
AIR (2007) [11]	18–65 years old FEV_1 60–85% Moderate/severe persistent asthma requiring ICS (> 200 μg/day beclomethasone) and long-acting beta-agonist (LABA; ≥ 100 μg/day of salmeterol) daily Presence of airway hyperresponsiveness Stable asthma 6 weeks before enrollment	BT group: 56 subjects Control group: 56 subjects	12 months	Difference in mean number of mild exacerbations from baseline was significant at 3 and 12 months for BT group, but not for control group (ten fewer mild exacerbations per subject per year in the BT group) No difference in number of severe exacerbations Significant improvements in morning PEF, AQLQ, ACQ, and percentage of symptom-free days within the BT group compared with the control group Greater response among those who required higher maintenance ICS (> 1000 μg/day beclomethasone or equivalent)	Increased adverse respiratory events periprocedure, with majority occurring within a day of the procedure Rates of hospitalization and adverse respiratory events were low and did not differ between groups in the post-treatment period
RISA (2007) [12]	18–65 years old FEV_1 ≥ 50% Presence of airway hyperresponsiveness Ex-smoker for at least a year, ≤ 10 pack-years smoking history On LABA (≥ 100 μg/day of salmeterol or equivalent) and ICS (> 750 μg/day fluticasone propionate or equivalent) ± prednisolone ≤ 30 mg/day	BT group: 15 subjects Control group: 17 subjects	12 months	Significant reduction in short-acting beta-agonist use from baseline among the BT group compared to control group Significant improvement in AQLQ and ACQ scores among the BT group compared to the control group 4/8 BT subjects versus 1/7 control subjects were able to wean off oral corticosteroids	Increased wheezing, chest discomfort, and cough among the BT group in the treatment period 136 respiratory adverse events in BT group (49% mild, 41% moderate, 10% severe) versus 57 respiratory adverse events in control group (49% mild, 47% moderate, 4% severe) during treatment period No increase in adverse events in the post-treatment period

Table 1 continued

Landmark papers	Study population	Number of subjects	Follow-up	Outcomes	Adverse events
AIR2 (2010) [13]	18–65 years old Ex-smoker for at least a year, ≤ 10 pack-years smoking history $FEV_1 \geq 60\%$ Severe asthma (AQLQ ≤ 6.25, ≥ 2 days of asthma symptoms during 4-week baseline) On LABA (≥ 100 µg/day of salmeterol or equivalent) and ICS (> 1000 µg/day beclomethasone or equivalent)	BT: 196 subjects Sham group: 101 subjects	12 months	79% of BT subjects had a clinically meaningful improvement of AQLQ score of ≥ 0.5 compared to 64% of the sham group Mean change in AQLQ in BT group (1.35 ± 1.10) was greater than the sham group (1.16 ± 1.23) 32% reduction in rate of severe group compared with sham group [26.3% (50/190) versus 39.8% (39/98) respectively] Significant sham effect was noted among the control group BT subjects reported fewer days lost from activities due to asthma Improved morning PEF, symptom-free days, ACQ, and rescue medication use in favor of BT group	During treatment period, 8.4% of BT subjects required hospitalization compared with 2.0% in the sham group During post-treatment period, 36% risk reduction in proportion of subjects reporting asthma worsening in BT group than in sham group During post-treatment period, 84% reduction in ED visits for respiratory symptoms in the BT group compared with the sham group

FEV_1 forced expiratory volume in the first second of the maneuver, *ICS* inhaled corticosteroid, *LABA* long-acting beta-agonist, *AQLQ* asthma quality of life questionnaire, *ACQ* asthma control questionnaire, *BT* bronchial thermoplasty, *ED* emergency department

airways of the right lower lobe, followed by left lower lobe, then both upper lobes separated 3 weeks apart. BT is effective in improving symptom control and reducing asthma exacerbations and visits to the emergency department (ED). Three randomized controlled trials (RCTs) from 2007 to 2010 demonstrated BT efficacy [11–13]. Respiratory-related events such as bronchospasm and radiographic pneumonitis occur within the first week of BT *(Table 1)*. After pivotal sham-controlled study that led to FDA approval, cohort studies with follow-up of 2, 5, and 10 years demonstrate sustained beneficial effects of BT [26–29] in reduced emergency room and hospital admissions, unscheduled physician visits, and corticosteroid prescriptions [26–30]. In addition, the improvements in asthma quality of life questionnaire (AQLQ) and asthma control questionnaire (ACQ) scores were sustained with a reduction in use of rescue inhalers. BT's safety profile remained reasonable. While 6/89 patients developed asymptomatic incidental radiological evidence of mild bronchiectasis, the underlying etiology is unclear and may not be secondary to BT [29]. At least 140 activations over the three procedures should be considered for maximum efficacy [29].

How Does Bronchial Thermoplasty Work?

While the full mechanism is yet unclear, BT's impact appears varied, going beyond decreasing the airway smooth muscle (ASM) and reticular basement membrane thickness in the proximal and distal airways. There is evidence of reduction in epithelial neuroendocrine cell, ASM-associated nerve, and submucosal nerve densities, and increase in epithelial integrity [31, 32]. It is likely that BT helps mediate the parasympathetic activation of the ASM as well as decrease airway wall thickness, thus reducing airway resistance with corresponding radiological and symptomatic improvement [33, 34].

In addition, emerging evidence suggests that BT also helps mediate airway inflammation, with a downregulation of eosinophils, cytokines [such as transforming growth factor-β_1 (TGF-β_1) and interleukin (IL)-33], chemokines [such as regulated upon activation, normal T-cell expressed and secreted (RANTES)/CCL5] and even epithelial type 2 (T2) inflammatory responses [35, 36]. This is further reaffirmed in TASMA, an international multicenter randomized controlled trial where patients with severe asthma were randomized to receive immediate or late BT [37]. While there was a substantial decrease in ASM, the treatment response appeared to correlate more with the IgE and eosinophil reduction rather than the baseline ASM mass [37]. The epithelial–mesenchymal interaction appears to further contribute to the reduction in airway remodeling through BT's ability to modulate the expression of epithelial.cell-derived heat shock protein 60 (HSP60), which helps regulates protein arginine methyltransferase-1 (PRMT1) and asthmatic fibroblasts [38].

Which Patients Would Benefit from Bronchial Thermoplasty?

The oft-quoted three RCTs were relatively conservative in the study population (Table 1) [11–13]. However, real-world studies often recruit patients who are sicker and do not completely conform to the study population. Performing BT among patients with severe asthma with FEV_1 30–50% still appears efficacious with no evidence of increased adverse effects [39]. Furthermore, comparing PAS2 (a prospective, multicenter observational study of patients with severe asthma conducted to assess the effectiveness and safety of BT published in 2017) [40] and AIR2 (a double-blinded trial of patients with severe asthma who were randomized to either the BT or sham groups to assess the efficacy of BT) [13], PAS2 participants were older and with more comorbidities and more PAS2 patients were taking maintenance oral corticosteroids. Yet, PAS2 participants were found to have responded equally well to BT as the participants in AIR2, with a slight increase in periprocedural respiratory-related adverse effects [40]. Similar to the other longitudinal studies, these patients continued to experience the benefits of BT with decreased exacerbations, ED visits, and hospitalizations 5 years postprocedure with no postprocedural safety concerns [41]. Thus, there may be a recalibration of considering sicker and more symptomatic patients for BT as they seem to derive the greatest benefit from BT [29, 42].

The PAS2 study also suggested that patients with eosinophilic endotype may respond favorably to BT, too [40, 41]. In the era of biologic agents [10], BT had assumed a more peripheral role, being offered to those who suffered from non-allergic asthma endotypes or those who were not eligible for or responded poorly to biologic agents. However, PAS2 suggests that a greater role may be available for BT among those with the eosinophilic endotype, and this was further reaffirmed in the TASMA study [37]. On the contrary, bronchodilator responsiveness does not appear to play a role in predicting BT response [43].

What Lies Ahead for Bronchial Thermoplasty?

Where BT lies in the management algorithm of severe asthma remains uncertain. Recent studies suggest that BT can be as efficacious as biologic agents, with activity against IL-5, IL-13, and IgE, in treating eosinophilic asthma, but this requires further validation [44, 45]. In

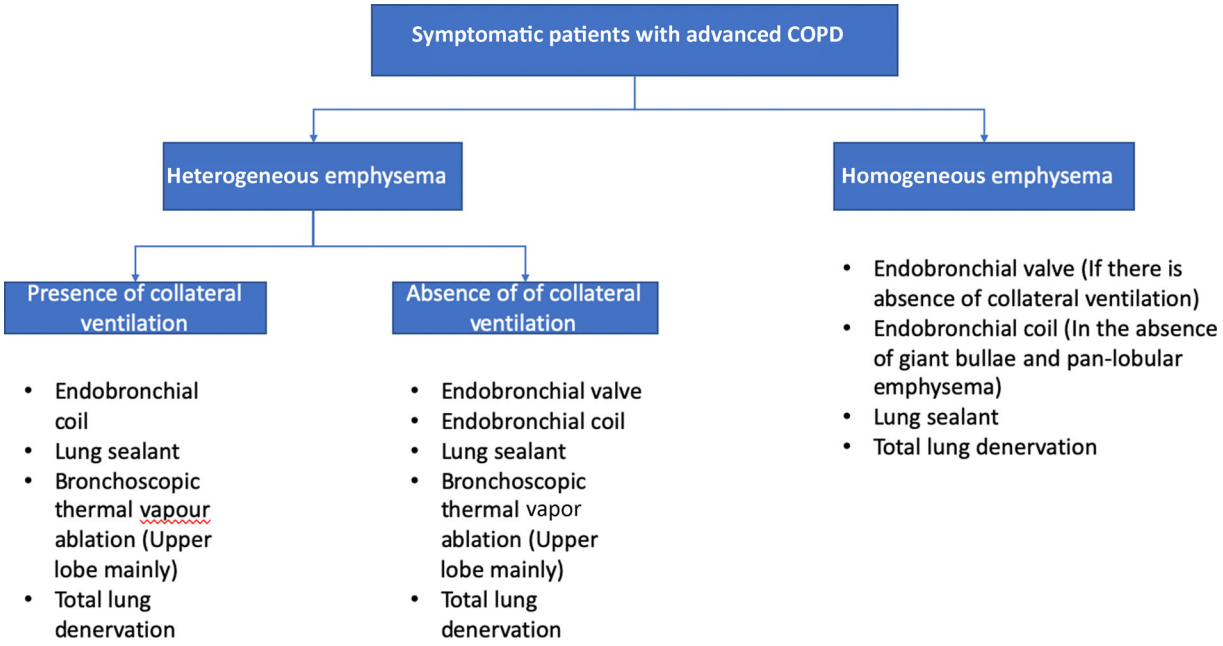

Fig. 1 Dichotomy of bronchoscopic lung volume reduction procedures

addition, the cost-effectiveness of BT compared with biologic agents remains unclear, which has limited its application and availability [46, 47]. One consideration to further refine the BT procedure includes utilizing magnetic resonance imaging to provide targeted BT implementation in one procedure with fewer periprocedural events [48]. At present, GINA 2022 has still limited the recommendation of performing BT within the confines of the study population characteristics in the RCTs for clinical work [9, 11–13].

ENDOSCOPIC THERAPY IN COPD

Studies have demonstrated that LVR helps (a) reduce hyperinflation, thus improving respiratory muscle kinetics, (b) increase lung elastic recoil and improve expiratory flow, and (c) reduce dead space and diversion of capillary bloods to areas with better ventilation, thus improving gaseous exchange [49]. Thus, less invasive LVR methods with lower complication rates were sought to accommodate a broader group of patients with COPD.

Creating transbronchial passageways with bronchial stents to relieve severe homogeneous emphysema are ineffective given the nonsustained improvements in lung function indices and symptoms in the EASE study [50]. However, other bronchoscopic LVR (BLVR) procedures such as endobronchial valve (EBV) therapy, endobronchial coil (LVRC), bronchial thermal vapor ablation (BTVA), lung sealants, and targeted lung denervation (TLD) have shown promise and are further elaborated below, with patient selection being the key consideration in mind (Fig. 1). Importantly, potential patients must have demonstrated the presence of hyperinflation via the body plethysmography as defined in the studies (Tables 2 and 3).

Endobronchial Valves

There are two different endoscopic valves that have been rigorously assessed in trials, namely the Zephyr endobronchial valve (Pulmonx Redwood City, CA, USA) and Spiration valve system (SVS) (Olympus, Redmond, WA, USA), formerly known as the intrabronchial valve. The intent of these EBVs is to function as

Table 2 Landmark papers on endobronchial valves

Landmark paper	Study population	Determining collateral ventilation status	Outcomes	Adverse events
Zephyr endobronchial valve (Pulmonx Redwood City, CA, USA)				
VENT (2010) [52]	40–75 years old FEV_1 15–45% TLC ≥ 100% RV ≥ 150% BMI < 31.1 (male), < 32.3 (female) 6MWD ≥ 140 m (had pulmonary rehab 6–8 weeks prior to randomization)	Fissure integrity (≥ 90% of the fissure is present on HRCT on at least one axis)	At 6 months FEV_1 increased 4.3% (EBV), while decreasing by 2.5% (control) 6MWD increased by 9.3 m (EBV), while decreasing by 10.7 m (control) However, among EBV group with complete fissures, results were as follows: FEV_1 increased 16.2% at 6 months and 17.9% at 12 months versus 2.0% and 2.8%, respectively No difference in 6MWD Among patients with median heterogeneity ≥ 15%, results were as follows: FEV_1 increased 10.7% at 6 months and 13.3% at 12 months versus 2.% and 1.5%, respectively Increase of 12.4 m at 6 months and 7.1 m at 12 months (trend towards significance, $p = 0.08$) versus −0.1 m and −0.6 m, respectively	6.1% (EBV) versus 1.2% (control) No survival difference Pneumonia, COPD exacerbation, hemoptysis were more common

Table 2 continued

Landmark paper	Study population	Determining collateral ventilation status	Outcomes	Adverse events
Euro-VENT (2012) [53]	40–75 years old FEV_1 15–45% TLC ≥ 100% RV ≥ 150% BMI < 31.1 (male), < 32.3 (female) 6MWD ≥ 140 m (had pulmonary rehab 6–8 weeks prior to randomization)	Fissure integrity (≥ 90% of the fissure is present on HRCT on at least one axis)	At 6 months FEV_1 increased 7 ± 20% (EBV) versus increased by 0.5 ± 19% (control) Cycle ergometry work load change [2 ± 14 W (EBV) versus −3 ± 10 W (control)] 6MWD surgical and endoscopic interventions that reduce lung volume for emphysema: a systemic review and meta-analysis increased by 15 ± 91 m (EBV) versus 10 ± 78 m (control) Change in SGRQ [−5 ± 14 points (EBV) versus 0.3 ± 13 points (control)] At 12 months FEV_1 increased 6 ± 26% (EBV) versus decreased by 2 ± 20% (control) Cycle ergometry work load change [1 ± 13 W (EBV) versus −5 ± 12 W (control)] Those with complete fissure and complete lobar occlusion had higher improvement in FEV_1, SGRQ and cycle ergometry workload at 6 and 12 months	Higher rates of pneumothorax among EBV cases
BeLieVeR-HIFi (2015) [57]	FEV_1 < 50% TLC ≥ 100%	Fissure integrity (≥ 90% complete)	FEV_1 increased by a mean 24.8% from baseline in the EBV group and 3.9% in the control group	No difference in COPD exacerbation Had greater incidence of pneumothorax
	RV ≥ 150% mMRC ≥ 3 6MWD < 450 m Ex-smoker on optimal therapy	Chartis pulmonary assessment system	EBV group had a significant improvement in 6MWD and T_{LIM} on cycle ergometry compared with control group SGRQ scores improved more in EBV group compared with the control group, but not statistically significant	

Table 2 continued

Landmark paper	Study population	Determining collateral ventilation status	Outcomes	Adverse events
STELVIO (2015) [60]	> 35 years old Stopped smoking for > 6 months	Complete or nearly complete fissure between target lobe and adjacent lobe on HRCT	At 6 months FEV_1, FVC, and 6MWD were significantly greater in EBV group than in control group	Pneumothorax frequency was 18%
	FEV_1 < 60% TLC ≥ 100% RV ≥ 150%		Improvement in SGRQ scores and CCQ scores greater among EBV group than in control group	Permanent removal of all valves in two patients
	mMRC ≥ 1 Deemed no collateral ventilation	Chartis pulmonary assessment system	Median change of TLVR was 1366 ml Effects were greater among patients with heterogeneous emphysema (emphysema destruction score ≥ 15%)	Repeat bronchoscopy in 35% of EBV group patients
IMPACT (2016) [61]	> 40 years old Stopped smoking for > 6 months FEV_1 15–45% TLC ≥ 100% RV ≥ 200% Homogeneous emphysema (emphysema destruction score ≤ 15%) + perfusion scintigraphy of ≤ 20% difference between right and left lung	Chartis pulmonary assessment system	At 3 months FEV_1 increased by 13.7 ± 28.2% (EBV), while it decreased by 3.2 ± 13.0% (control) Better SGRQ and 6MWD results among the EBV group TLVR was −1195 ± 683 ml, compared with baseline	Pneumothorax frequency was 25.6%
TRANSFORM (2017) [58]	> 40 years old Stopped smoking for > 6 months FEV_1 15–45% TLC ≥ 100% RV ≥ 180% 6MWD of 150-450 m	Chartis pulmonary assessment system	Responder (≥ 12% improvement in FEV_1) rate was 55.4% (EBV) versus 6.5% (control) at 3 months, and 56.3% (EBV) versus 3.2% (control) Significantly higher number of patients in the EBV group met the MCID for FEV_1, 6MWD, and SGRQ at 6 months	At 6 months, 47.7% of subjects in EBV group suffered adverse events compared with 9.4% of subjects in the control group 29.2% of patients suffered pneumothorax

Table 2 continued

Landmark paper	Study population	Determining collateral ventilation status	Outcomes	Adverse events
LIBERATE (2018) [59]	40–75 years old Stopped smoking for > 6 months FEV_1 15–45% TLC ≥ 100% RV ≥ 175% 6MWD of 100–500 m	Chartis pulmonary assessment system	At 12 months, 47.7% of EBV group had a ≥ 15% increase in post-BD FEV_1 compared with 16.8% of the control group The EBV group improved significantly in terms of the FEV_1, 6MWD, SGRQ, and mMRC compared with the control group. They were seen as early as 45 days postprocedure 84.2% of EBV group achieved TLVR ≥ 350 ml, with 61.6% of EBV group achieving reduction in RV of > 310 ml More control-group subjects required supplementary oxygen compared with EBV subjects Similar benefits seen in both upper- and lower-lobe subgroups	35.2% (EBV group) had respiratory adverse effects compared with 4.8% (control group) up to 45 days Comparable event frequency thereafter up to a year Pneumothorax frequency was 34.4%
Spiration valve system (SVS) (Olympus, Redmond, WA, USA), formerly known as the intrabronchial valve				
Ninane colleagues (2012) [93]	40–75 years old Stopped smoking for > 4 months FEV_1 ≤ 45% TLC ≥ 100% RV ≥ 150% 6MWD of 100–500 m Predominantly upper lobe emphysema on CT	Nil	24% (8/33) of the treatment group exceeded the minimum threshold changes for CT lung volumes (upper lobe volume decrease with compensatory volume increase in nontreated lobes of ≥ 7.5%) and SGRQ compared with 0% (0/35) of the control group Further improvement in SGRQ in the treatment group was sustained at 6 months	No difference in adverse events. No pneumothorax reported
IBV (2014) [94]	40–74 years old Significant dyspnea Upper lobe predominant emphysema on CT and lung perfusion scans < 2 hospitalizations for COPD exacerbation in the prior year	Nil	5.0% (6/121) of the treatment group were responders by SGRQ (≥ 4 point reduction from baseline) and CT lobar volume change (≥ 10% increase in non-upper lobe volume and decrease in upper lobe volume) criteria compared with 0.7% (1/134) of the control group	14.1% of the treatment groups suffered adverse events, compared with 3.7% of the control group There were more COPD exacerbations and pneumothoraces in the treatment group

Table 2 continued

Landmark paper	Study population	Determining collateral ventilation status	Outcomes	Adverse events
REACH (2019) [62]	$FEV_1 \leq 45\%$ TLC $\geq$ 100% RV $\geq$ 150% HRCT demonstrating $\geq$ 40% emphysema involvement, high heterogeneity compared with adjacent ipsilateral lobe ($\geq$ 15% difference) and intact lobar fissure	Fissure integrity ($\geq$ 90% complete)	Mean FEV_1 improvement of 0.104 $\pm$ 0.178 L (EBV group) versus 0.003 $\pm$ 0.147 L (usual care group) at 3 months Higher responder rate among EBV group compared with usual group of achieving $\pm$ 15% improvement in FEV_1 TLVR of $\geq$ 350 ml achieved by the EBV group (52.5% and 66.1% of the population at the 3- and 6-month timepoints) At 3 and 6 months, SGRQ improved with statistical significance among the EBV group compared with usual care group 6MWD improved and achieved statistical significance only at 6 months	Overall serious adverse events rate was 33%, predominantly due to COPD exacerbations 7.6% rate of pneumothorax, which occurred mainly within 60 days of the procedure
EMPROVE (2019) [63]	$\geq$ 40 years old $FEV_1 \leq 45\%$ TLC $\geq$ 100% RV $\geq$ 150% HRCT demonstrating $\geq$ 40% emphysema involvement, high heterogeneity compared with adjacent ipsilateral lobe ($\geq$ 10% difference) and intact lobar fissure	Fissure integrity ($\geq$ 90% complete with no segmental vessels crossing between adjacent lobes)	Sustained FEV_1 improvements at 6 and 12 months among the EBV group compared with the control group Between-group difference in FEV_1 responder rate was 30.4% (EBV group) versus 25.7% (control group) At 6 months, 75% of EBV group achieved meaningful TLVR ($\geq$ 350 ml), with significantly greater mean RV/TLC improvement and SGRQ compared with the control group No statistically significant difference in 6MWD between both EBV and control groups	12.4% incidence of pneumothorax (majority occurred within 3 days of the procedure) Incidence of thoracic serious adverse events At 6 months, it was 31.0% (EBV group) versus 11.9% (control group) At 12 months, it was 21.4% (EBV group) versus 10.6% (control group) No difference in non-thoracic adverse events

FEV_1 forced expiratory volume in the first second of the maneuver, *TLC* total lung capacity, *RV* residual volume, *BMI* body mass index, *6MWD* 6-min walk distance, *mMRC* modified medical research council scale, *HRCT* high-resolution computed tomography scan of the thorax, *EBV* endobronchial valve, *SGRQ* St George's respiratory questionnaire, *TLVR* total lung volume reduction

Table 3 Landmark papers for endobronchial coils

Landmark study	Study population	Outcomes	Adverse events
RESET (2013) [70]	≥ 35 years old $FEV_1 \leq 45\%$	Greater improvement in SGRQ at 90 days among LVRC group versus usual care group	Six serious adverse events among LVRC group compared with one in the usual care group within 30 days post-treatment. Mainly LRTI and COPD exacerbation (self-limiting)
	TLC ≥ 100% RV ≥ 150%	Greater improvement in FEV_1 and RV reduction among LVRC group versus usual care group	
	mMRC ≥ 2 Stopped smoking for ≥ 8 weeks before enrollment	Clinically significant improvement in 6MWT at 90 days achieved more among LVRC groups versus usual care group	Two pneumothorax in the LVRC group
Zoumot and colleagues (2015) [72]	≥ 35 years old $FEV_1 \leq 45\%$ TLC ≥ 100% mMRC ≥ 2	Improvement of SGRQ sustained among the LVRC group up to 360 days	9.5% of all procedures had LRTI or COPD exacerbation in the first 30 days postprocedure
	Stopped smoking for ≥ 8 weeks before enrollment	Sustained improvement in 6MWT up to 360 days among the LVRC group	8 pneumothorax were seen in the LVRC group, predominantly within 4 h of procedure
	HRCT indicating emphysema (homogeneous or heterogeneous, unilateral or bilateral)	RV and RV/TLC ratio were significantly reduced at all timepoints among the LVRC group	
REVOLENS (2016) [73]	$FEV_1 \leq 50\%$ RV ≥ 220%	36% (18/50) in LVRC versus 18% (9/50) achieved a 6MWT distance improvement of ≥ 54 m at 6 months	No statistically significant difference in serious adverse event (most common even is pneumonia)
	Bilateral emphysema Completed pulmonary rehabilitation within the last year	Improvement in FEV_1, FVC, RV, RV/TLC, mMRC, and SGRQ greater among the LVRC group compared with the usual care group	No difference in deaths Most frequent nonserious adverse events is self-resolving hemoptysis

Table 3 continued

Landmark study	Study population	Outcomes	Adverse events
		At 12 months, the sustained improvement in 6MWT was not significant among LVRC compared with usual care group. Sustained improvement in FEV_1, FVC, RV, RV/TLC, mMRC, and SGRQ greater among the LVRC group compared with the usual care group at 12 months	
		No difference regarding efficacy between homogeneous and heterogeneous emphysema	
		36% (18/50) in LVRC versus 18% (9/50) achieved a 6MWT distance improvement of $\geq$ 54 m at 6 months	
RENEW (2016) [71]	$>$ 35 years old $FEV_1 \leq 45\%$	Median 6MWT change of 10.3 m at 12 months in the LVRC group versus −7.6 m in the usual care group	No difference in deaths
	TLC $\geq$ 100% RV $\geq$ 225%—> 175%[a] Stopped smoking	Greater improvement in SGRQ total score at 12 months among LVRC compared with usual care group	More complications in LVRC group due to increased LRTI
	Completed pulmonary rehabilitation	Change in FEV_1 was 3.8% (LVRC) versus −2.5% (usual care) at 12 months	
		Those with RV $\geq$ 225% and heterogeneous emphysema group had greater magnitudes of treatment responses	
		Greater response among those who had developed coil-associated opacities or pneumonia	

LVRC lung volume reduction coils, *FEV_1* forced expiratory volume in the first second of the maneuver, *TLC* total lung capacity, *RV* residual volume, *BMI* body mass index, *6MWT* 6-min walk test, *mMRC* modified medical research council scale, *LVRC* lung volume reduction coils, *SGRQ* St George's respiratory questionnaire, *LRTI* lower respiratory tract infection

[a]Lowered the RV threshold to address the effectiveness and safety of endobronchial coils in a broader patient population

unidirectional valves that permits air to only leave the treated lung and prevent re-entry, resulting in lobar collapse and reduce gas trapping [51].

As the best studied BLVR, initial studies were disappointing. The Endobronchial Valve for Emphysema Palliation Trial (VENT) only produced statistically significant improvement in the FEV_1 (6.8%) and 6-min walking distance (6MWD) (5.7%) between the EBV and control groups at 6 months, which failed to meet the minimal clinically important difference (MCID) [52]. However, subgroup analysis identified a "responder" phenotype, where patients with higher heterogeneity scores (defined as $\geq$ 15%) and intact interlobar fissures had greater response. This was further corroborated in the EURO-VENT analysis, and the effects were sustained up to 12 months. [53]

As such, studying the high-resolution computed tomography (CT) scan of the thorax is essential in assessing (a) the interlobar fissure integrity, (b) the lobar distribution of emphysema, and (c) the emphysema score and heterogeneity. Fissure integrity has been heavily emphasized as incomplete fissures may signify collateral ventilation (CV), which represent airflow between the lobes that bypass the normal bronchial tree [54]. The expert panel recommends that fissure completeness of $> 95\%$ suggest high success rate with lack of CV [55]. However, assessing fissure integrity requires either advanced computer software analysis or extremely detailed close visual analysis of all three orthogonal planes, which may not always be available [55]. The Chartis pulmonary assessment system is thus complementary. A catheter with a distal tip balloon is inserted and inflated at the target airway ostium during bronchoscopy. Air is then able to flow out from the target lobe only through the Chartis catheter central lumen. By integrating with a Chartis console, the CV status can be determined [56]. Studies have shown the greater reliability of the Chartis over CT assessment in determining CV status [57]. Since then, Chartis has become the key determinant of CV status in later trials [55–61].

The emphysema score quantifies the severity and distribution of emphysema in a quantifiable manner, being expressed as a percentage of voxels in each lobe below certain attenuation (HU) thresholds, which are usually −950 HU for thick-sliced CT scans and −950 HU in 1-mm noncontrasted chest CT scans [55]. Heterogeneity index is then determined, whereby the difference in emphysema percentage between ipsilateral lobes in the treated lung is assessed. An arbitrary cutoff of 10–15% has been used [52, 53, 58, 59, 62, 63].

The landmark STELVIO trial thereafter proved that, with careful selection of patients with COPD without CV (as assessed by Chartis), lung function indices, effort tolerance, and quality of life improved significantly and these effects were sustained up to a year postprocedure [60, 64]. The median change of total lung volume reduction (TLVR) was 1366 ml, far greater than the MCID of $\geq$ 350 ml and the volumes achieved in VENT [52, 53, 60]. This was further corroborated by the TRANSFORM [58] and LIBERATE trials [59]. Even without Chartis, utilizing CT to assess fissure integrity purely in EMPROVE still resulted in similar clinical findings up to 6 months [63] (Table 2).

Given that most EBV studies' study population comprised mainly heterogeneous emphysematous patterns, the IMPACT study sought to elucidate the benefit of EBV among those patients with COPD with homogeneous emphysema pattern. There is statistically and clinically significant improvement in the lung function indices, exercise tolerance, and quality of life even among patients with COPD with homogeneous emphysema, albeit of a smaller magnitude compared with those with heterogeneous emphysema [61].

Adverse events of EBV would include COPD exacerbation, pneumothorax and pneumonia. Of concern, pneumothorax appears to occur frequently at rates of 20–30%. However, some are ex-vacuo pneumothoraces, while up to 50% do not progress and are conservatively treated [52, 57–61, 64]. Pneumothorax usually occurs within the first 3 days postprocedure [65]. Thus, existing clinical protocols require these patients to remain in hospital for a similar duration with daily chest radiographs [65]. It is postulated that the rapid target lobe deflation and pleural adhesion may contribute to the higher

pneumothorax incidence [55], but these patients ultimately achieve excellent TLVR and have sustained clinical improvement [65]. In addition, despite the prolonged hospital stay, the cost-effectiveness profile of EBV treatment remains favorable compared with other treatment modalities such as LVRS and lung transplant [66]. It remains to be seen if EBV will supersede LVRS as the treatment modality of choice. The CELEB study comparing LVRS and EBV is now ongoing and will hopefully provide clarity [67].

Endobronchial Coils

LVRCs are deployed in the subsegmental airways. They comprise shape-memory non-occlusive nitinol coils that return to their predetermined shape after deployment, thus compressing on the diseased lung parenchyma and tethering open the airways [68]. They promote lung volume reduction (particularly the residual volume) [67], prevent dynamic hyperinflation, reestablish small airway tension, and improve elastic lung recoil [70–73]. Unlike endobronchial valves, LVRCs can be deployed regardless of the collateral ventilation status. They appear to be cost-effective in the long term, although the first-year incremental cost-effectiveness ratio is rather exorbitant [73, 74].

First described in 2010 [75], the initial small studies demonstrated short-term efficacy in terms of effort tolerance, symptoms, and lung function indices [68]. Subsequent randomized studies substantiated these findings, where there was sustained improvement in St George's respiratory questionnaire (SGRQ) scores, FEV_1, residual volume (RV), and 6MWD up to 2 years [70–73, 76] (Table 3). The safety profile is preferable compared with LVRS, with self-limiting mild hemoptysis, COPD exacerbations, pneumonia, and pneumothoraces (usually within hours of the procedure) [72] being the commonest adverse events [68]. Those who develop coil-associated opacities/pneumonia appear to be the best responders to the treatment [76].

Ideally, patients with advanced COPD ($FEV_1 \leq 45\%$ with $RV > 200\%$) who remain symptomatic [modified medical research council (mMRC) > 1 with 6MWD 140–450 m] are ideal candidates [68]. Importantly, LVRCs have been touted as a potential solution among those patients with COPD with homogeneous emphysema distribution. However, the RENEW study suggests that those with $RV \geq 225\%$ and heterogeneous emphysema distribution will still derive the greatest benefit from this endoscopic modality [71]. In addition, EBV may still be superior to LVRC in terms of improving 6MWD among COPD patients with homogeneous emphysema. Longer-term studies are eagerly awaited, with at least eight studies in the pipeline. [77]

Bronchoscopic Thermal Vapor Ablation

BTVA is an irreversible bilateral segmental bronchoscopic approach whereby heated water vapor is instilled to initiate a thermal reaction and localized inflammation, thereby leading to volume reduction of the emphysematous areas [78]. Importantly, there is heterogeneity within the targeted treatment lobe, with healthy and disease segments co-existing [79]. Unlike other endobronchial therapies, BTVA is unique in targeting only the diseased segments within the treatment lobe.

Patients with predominantly upper-lobe emphysematous COPD, ≤ 3 COPD-related hospitalizations in the last year, $FEV_1 \leq 45\%$, $RV \geq 175\%$, DLCO ≥ 20%, 6MWD 140–500 m, and no recent history of myocardial infarction may be considered for BTVA under existing research protocols. Those with pulmonary hypertension and left ventricular ejection fraction of < 40% were excluded [78].

At a lobar vapor dose of 8.5–10 cal/g over sequential sessions, BTVA is able to achieve lobar volume reduction with corresponding improvement in the lung function indices, exercise tolerance, and quality of life up to a year [80–82]. This also remains independent of collateral ventilation status [80–82]. Main adverse events postprocedure would be COPD exacerbation and pneumonia [78].

Lung Sealant

Application of biological adhesives within the targeted airways was aimed to deactivate surfactant and promote local atelectasis, induce local inflammatory response and form fibrotic tissue, thus shrinking the hyperinflated lung [83]. Autologous blood and AeriSeal were touted as potential bio-adhesives.

Unfortunately, autologous blood fell out of favor quickly owing to poor efficacy and the propensity for pneumonia development [84, 85]. On the other hand, AeriSeal—a polymeric foam—had demonstrated significant efficacy in reducing lung volume and improving lung function indices, exercise tolerance, and quality of life, which was sustained at 6 months, albeit at the substantial risk of pneumonia within 90 days of the procedure [86]. This has limited clinical utility. However, AeriSeal may be effective in blocking collateral ventilation in conjunction with EBV treatment [87]. Exploratory studies are ongoing (NCT04256408 and NCT04559464).

Targeted Lung Denervation

Bronchoconstriction and airway inflammation are mediated by the parasympathetic airway nerve fibers. TLD aims to disrupt the peribronchial vagal lung innervation via radiofrequency ablation under fluoroscopic guidance. It is not dependent on collateral ventilation status or emphysema pattern and appears to be suitable for symptomatic patients with advanced COPD (FEV_1 30–60%, mMRC ≥ 2 or CAT score ≥ 10). [88]

Several pilot studies have demonstrated that TLD led to a reduction in COPD respiratory adverse events, in particular severe COPD exacerbations, over a year [88–90]. There are some suggestions of improved lung function indices, effort tolerance, and symptoms [88–90] and appear to be sustained up to 3 years post-procedure [91, 92]. The main concern would be the development of increased gastrointestinal events due to damage to the vagal esophageal plexus in the process of conducting TLD [88]. Larger-scale studies are required to validate these findings.

CONCLUSION

Despite the medical advances in the armamentarium of asthma and COPD therapies, endoscopic procedures still have an important role to play in the management of airway diseases. The emerging evidence supports the sustained efficacy of BT among patients with severe asthma. Given BT's ability to reduce ASM and mediate airway inflammation concurrently, there is great potential for BT to play a larger role among the patients with more severe asthma with eosinophilic endotype, although some caution should be exercised given the suggestion of possible development of mild bronchiectasis. In addition, the myriad of endoscopic therapies for patients with advanced COPD appear appealing, given the limited clinical utility of LVRS. Patients with advanced COPD ideally should undergo body plethysmography, so as to identify those with significantly high RV and potentially qualify for endobronchial intervention. Endobronchial valves and endobronchial coils remain the best-studied options and are already recommended for clinical use in selected groups of patients with COPD.

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