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► **To cite this version:**

Jeanne-Marie Perotin, Maxime Dewolf, Claire Launois, Valérian Dormoy, Gaëtan Deslee. Bronchoscopic management of asthma, COPD and emphysema. *European Respiratory Review*, 2021, 30 (159), pp.200029. 10.1183/16000617.0029-2020 . hal-03194039

HAL Id: hal-03194039

<https://hal.univ-reims.fr/hal-03194039>


Submitted on 22 Jan 2024

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Bronchoscopic management of asthma, COPD and emphysema

Jeanne Marie Perotin^{1,2}, Maxime Dewolf¹, Claire Launois¹, Valérien Dormoy^{1,2} 
and Gaëtan Deslee^{1,2}

Number 6 in the Series “Interventional pulmonology”
Edited by David Feller-Kopman and Hervé Dutau

Affiliations: ¹Dept of Pulmonary Medicine, University Hospital of Reims, Reims, France. ²INSERM P3Cell UMR-S1250, SFR CAP-SANTE, University of Reims Champagne Ardenne, Reims, France.

Correspondence: Gaëtan Deslee, Dept of Pulmonary Medicine, University Hospital of Reims, 45 rue Cognacq-Jay, 51092 Reims Cedex, France. E-mail gdeslee@chu-reims.fr

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Many therapeutic bronchoscopic techniques have been recently developed including bronchial thermoplasty in asthma, and valves, coils and thermal vapor ablation in emphysema, and targeted lung denervation in COPD <https://bit.ly/2VhMsDI>

Cite this article as: Perotin JM, Dewolf M, Launois C, *et al.* Bronchoscopic management of asthma, COPD and emphysema. *Eur Respir Rev* 2021; 30: 200029 [<https://doi.org/10.1183/16000617.0029-2020>].

ABSTRACT In recent years, many bronchoscopic techniques have been developed in chronic obstructive airway inflammatory diseases, including asthma, COPD and emphysema. The main techniques with available data from randomised controlled trials are: 1) bronchial thermoplasty in asthma; 2) valves, coils and thermal vapor ablation in emphysema; and 3) targeted lung denervation in COPD. The objectives of this article are to describe the levels of evidence for efficacy and safety, long-term follow-up results beyond 1 year, and current recommendations for clinical practice from international guidelines for each technique.

Introduction

The field of interventional bronchoscopy in chronic obstructive airway inflammatory diseases including asthma, COPD and emphysema has greatly evolved in recent years. Many bronchoscopic techniques have been developed and assessed initially in nonrandomised studies, with promising results raising hope and excitement for the management of these challenging patients. In the past 15 years, several randomised controlled trials (RCT) have been conducted allowing the ability to determine the levels of evidence for each technique. In this article, we focus on bronchoscopic techniques with available data from RCTs including: 1) bronchial thermoplasty in asthma; 2) valves, coils and thermal vapor ablation in emphysema; and 3) targeted lung denervation in COPD.

The aims of this article are to describe the following for each technique: 1) the levels of evidence for efficacy and safety based on RCTs results; 2) long-term follow-up results beyond 1 year from RCTs or

Provenance: Commissioned article, peer reviewed.

Previous articles in this series: **No. 1:** DeMaio A, Sterman D. Bronchoscopic intratumoral therapies for nonsmall cell lung cancer. *Eur Respir Rev* 2020; 29: 200028. **No. 2:** Chandrika S, Yarmus L. Recent developments in advanced diagnostic bronchoscopy. *Eur Respir Rev* 2020; 29: 190184. **No. 3:** Kniese CM, Musani AI. Bronchoscopic treatment of inoperable nonsmall cell lung cancer. *Eur Respir Rev* 2020; 29: 200035. **No. 4:** Rosell A, Stratakos G. Therapeutic bronchoscopy for central airway disease. *Eur Respir Rev* 2020; 29: 1900178. **No. 5:** Bedawi EO, Guinde J, Rahman NM, *et al.* Advances in pleural infection and malignancy. *Eur Respir Rev* 2021; 30: 200002.

Received: 31 Jan 2020 | Accepted after revision: 15 June 2020

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“real-life” studies when available; and 3) current recommendations for clinical practice from international guidelines.

Asthma

Bronchial thermoplasty is a bronchoscopic procedure performed under general anaesthesia or conscious sedation that delivers controlled thermal energy to the airway wall during a series of bronchoscopy procedures (three procedures in the main RCTs), resulting in a prolonged reduction in airway smooth muscle mass [1, 2] thought to improve bronchoconstriction in asthma [3].

Levels of evidence

The results of three RCTs have been published [4–6] and long-term analysis 5 years after treatment are available for two of these RCTs (table 1) [7, 8].

The AIR study [4] included 112 subjects randomised to bronchial thermoplasty (n=56) or medical management (control, n=56). Subjects had moderate to severe asthma, with forced expiratory volume in 1s (FEV₁) 60–85% of the predicted value and worsening of symptoms on long-acting β -agonist (LABA) withdrawal. No sham procedure was performed. Outcome assessment at 12 months identified a decrease in the number of mild exacerbations, improvement in peak expiratory flow (PEF), asthma control questionnaire (Asthma Quality of Life Questionnaire (AQLQ) and Asthma Control Questionnaire (ACQ)) scores, symptom-free days and rescue medication use. No significant changes in FEV₁, airway responsiveness (AHR) or number of severe exacerbations were observed.

The RISA trial [5] focused on people with severe asthma, defined as requiring high-dose inhaled corticosteroids (ICS) and LABAs with or without oral prednisone, leukotriene modifiers or theophylline. Other inclusion criteria were FEV₁ \geq 50% pred and AHR. Subjects were randomised to bronchial thermoplasty (n=15) or medical management (control, n=17). In the bronchial thermoplasty group, after a 16-week ICS dose-stability phase, ICS dose was reduced. Assessment 52 weeks after treatment identified a reduction in rescue medication use and improvement in ACQ and AQLQ scores. FEV₁ and AHR were not modified.

The AIR2 trial [6] included 288 people with severe asthma (high-dose ICS+LABA) randomised to bronchial thermoplasty (n=190) or sham control (n=98). Subjects had FEV₁ \geq 60%, AHR and AQLQ \leq 6.25. Outcome assessment performed 12 months after treatment showed improved AQLQ score and decrease in the number of severe exacerbations, emergency department visits and days lost from work/school. No change in PEF, ACQ score, number of symptom-free days, frequency of rescue medication use and rates of hospitalisation was noted. Of note, a substantial sham effect was described in this study including a clinically meaningful improvement in AQLQ score (\geq 0.5) in 64% of the sham group (79% in bronchial thermoplasty group, posterior probability of superiority 99.6%) and a mean improvement of 1.16 in AQLQ in the sham group (1.35 in the bronchial thermoplasty group, posterior probability of superiority 96.0%). This unexpected placebo effect was discussed as resulting from preconceived expectations and the care and attention provided by the study staff.

In all three RCTs, bronchial thermoplasty procedure was associated with frequent immediate and transient worsening of asthma symptoms [4–6]. Consolidation, atelectasis and upper or lower respiratory tract infections were also reported.

Overall, these three RCTs suggest a beneficial impact of bronchial thermoplasty on asthma control and quality of life with an acceptable safety profile. However, one limitation is that a sham group has been conducted in only one study, which showed a substantial sham effect. The criteria of inclusion in these three studies are somewhat heterogeneous, but selected mainly severe asthma with relatively similar patients' characteristics. The primary end-points are very heterogeneous based on exacerbation, safety or asthma control questionnaires, making the comparison between these RCTs difficult.

The grading of recommendations, assessment, development and evaluations (GRADE) for bronchial thermoplasty from these three RCTs is moderate with a low risk of bias, low risk of imprecision, consistency of efficacy results but limited to three RCTs, no evident indirectness, and no known publication bias.

Long-term follow-up results

Long-term analysis (5 years) of the AIR study [7] included 45 subjects in the bronchial thermoplasty group and 24 controls and identified improvement of AHR up to 3 years after bronchial thermoplasty. No clinical complications, increase in hospitalisations or emergency department visits, or increased adverse events beyond 1 year were noted, whereas FEV₁ remained stable. The analysis of the AIR2 study performed 5 years after treatment included 162 subjects in the bronchial thermoplasty group [8] and identified a sustained reduction in the number of exacerbations and emergency department visits. The authors noted an 18%

TABLE 1 Characteristics of randomised controlled trials

Study [Ref.]	Subjects N	Main inclusion criteria	Control group	Primary end-point
Asthma: BT				
AIR [4]	BT: 56; control: 56	Moderate/severe asthma, worsening control on LABA withdrawal, FEV ₁ 60–85%	Usual care	Frequency of mild exacerbations at 3, 6, 12 months Primary end-point results: change in frequency per subject per week from baseline: -0.16 ± 0.37 in BT group <i>versus</i> 0.04 ± 0.29 in control group, $p=0.005$
RISA [5]	BT: 15; control: 17	Severe asthma, FEV ₁ $\geq 50\%$	Usual care	Safety: adverse events Primary end-point results: 136 respiratory adverse events in BT group (49% mild, 41% moderate, 10% severe) <i>versus</i> 57 respiratory adverse events in control group (49% mild, 47% moderate, 4% severe)
AIR2 [6]	BT: 196; control: 101	Severe asthma, FEV ₁ $\geq 60\%$	Sham	Integrated AQLQ score at 6, 9, 12 months Primary end-point results: change in integrated AQLQ score: 1.35 ± 1.10 in BT group <i>versus</i> 1.16 ± 1.23 in control group; posterior probability of superiority 96.0%
Emphysema: endobronchial lung volume reduction				
Valve: EBV or SVS				
BeLieVeR-HIFI [9]	EBV: 25; control: 25	FEV ₁ <50%, RV >150%, heterogeneous, collateral ventilation assessed by CT scan (visual)	Sham	Percentage change FEV ₁ at 3 months Primary end-point results: FEV ₁ 8.77% (IQR 2.27–35.85) in EBV group <i>versus</i> 2.88% (IQR 0–8.51) in control group ($p=0.03$)
STELVIO [10]	EBV: 34; control: 34	FEV ₁ <60%, RV >150%, heterogeneous and homogeneous, collateral ventilation assessed by CT scan (visual) and Chartis	Usual care	Improvement from baseline in FEV ₁ , FVC, and 6MWT at 6 months Primary end-point results: FEV ₁ : 20.9% (95% CI 11.1–30.7) in EBV group <i>versus</i> 3.1% (95% CI -0.4 to 6.6) in control group, difference between group 17.8% (95% CI 7.6–28.0), $p=0.001$; FVC: 18.3% (95% CI 9.3–27.3) in EBV group <i>versus</i> 4.0% (95% CI -0.7 –8.6) in control group, difference between group 14.4% (95% CI 4.4–24.3), $p=0.005$; 6MWT: 19.6% (95% CI 10.4–28.9) in EBV group <i>versus</i> -3.6 (95% CI -6.9 –0.4), difference between group 23.3 (95% CI 13.6–32.9), $p<0.001$
IMPACT [11]	EBV: 43; control: 50	15% < FEV ₁ < 45%; RV >200%, homogeneous, collateral ventilation assessed by Chartis	Usual care	Percentage change FEV ₁ at 3 months Primary end-point results: FEV ₁ : $13.7 \pm 28.2\%$ in the EBV group <i>versus</i> $-3.2 \pm 13.0\%$ in control group; mean difference between groups of 17.0% (95% CI 8.1–25.8%, $p=0.0002$)
TRANSFORM [12]	EBV: 65; control: 32	15% < FEV ₁ < 45%; RV >180%, heterogeneous, collateral ventilation assessed by Chartis	Usual care	Percentage subjects with $\geq 12\%$ improvement from baseline in FEV ₁ at 3 months Primary end-point results: 55.4% in the EBV group; 6.5% in the control group ($p=0.001$)
LIBERATE [13]	EBV: 128; control: 62	15% < FEV ₁ < 45%; RV >175%, heterogeneous, collateral ventilation assessed by Chartis	Usual care	Percentage subjects with $\geq 15\%$ improvement from baseline in FEV ₁ at 12 months Primary end-point results: 47.7% in the EBV group; 16.8% in the control group; between-group absolute difference of 31.0 (95% CI 18.0–43.9%; $p=0.001$)
REACH [14]	SVS: 66; control: 33	FEV ₁ $\leq 45\%$, RV $\geq 150\%$, heterogeneous, intact interlobar fissure assessed by CT scan (visual)	Usual care	Difference between groups in mean change FEV ₁ at 3 months Primary end-point results: FEV ₁ 0.104 ± 0.18 L in SVS group <i>versus</i> 0.003 ± 0.15 L in control group, $p=0.001$
EMPROVE [15]	SVS: 113; control: 59	FEV ₁ <45%, RV >150%, heterogeneous, intact interlobar fissure assessed by CT scan (visual)	Usual care	Difference between groups in mean change FEV ₁ at 6 months Primary end-point results: FEV ₁ 0.099 L (95% CI 0.069–0.128) in SVS group; 0.002 L (95% CI 0.030–0.026); between-group difference 0.101 L (95% CI 0.060–0.141)
Coils				
RESET [16]	Coil: 23; control: 24	FEV ₁ $\leq 45\%$, homogeneous and heterogeneous	Usual care	Difference in quality of life (SGRQ) between both groups at 90 days Primary end-point results: SGRQ: -8.11 (-13.83 – -2.39) in coil group; 0.25 (-5.58 – 6.07) in control group; between-group difference: -8.36 (-16.24 – -0.47), $p=0.04$

Continued

TABLE 1 Continued

Study [Ref.]	Subjects N	Main inclusion criteria	Control group	Primary end-point
REVOLENS [17]	Coil: 50; control: 50	FEV ₁ <50%, RV ≥220%, homogeneous and heterogeneous, formal pulmonary rehabilitation within 12 months	Usual care	Percentage of subjects with 6MWT ≥54 m at 6 months
	Primary end-point results: 36% in coil group; 18% in control group; between-group difference: 18% (one-sided 95% CI 4% to ∞; p=0.03)			
RENEW [18]	Coil: 157; control: 158	FEV ₁ <45%, RV ≥225% (lowered to ≥175% after enrolment of 169 patients), homogeneous and heterogeneous	Usual care	Difference in the 6MWT changes between groups at 12 months
	Primary end-point results: 10.3 m in coil group; -7.6 m in control group; between-group difference: 14.6 m [97.5% CI 0.4 m to ∞; one-sided p=0.02]			
TVA				
STEP-UP [19]	TVA: 46; control: 24	FEV ₁ 20–45%, heterogeneous upper lobe predominant emphysema	Usual care	Changes in FEV ₁ and quality of life (SGRQ) between groups at 6 months
	Primary end-point results: FEV ₁ : 11.0±16.2% in TVA group; -3.7±11.1% in control group; difference between group: 14.7% [95% CI 7.8–21.5], p<0.0001 SGRQ: -9.7±14.4 in TVA group; -0.0±9.8 in control group; difference between groups -9.7 [95% CI -15.7–-3.7], p=0.0021			
COPD: TLD				
AIRFLOW-2 [20]	TLD: 41; control: 41	FEV ₁ 30–60%, symptomatic COPD (mMRC ≥2 or CAT ≥10)	Sham	Safety: difference between groups in respiratory adverse events at 3–6.5 months
	Primary end-point results: 32% in TLD group <i>versus</i> 71% in control group, p=0.008; OR 0.19 [95% CI 0.0750–0.4923], p=0.0006			

BT: bronchial thermoplasty; EBV: endobronchial valve; SVS: Spiration valve system; TVA: thermal vapor ablation; TLD: targeted lung denervation; LABA: long-acting β-agonist; FEV₁: forced expiratory volume in 1 s; AQLQ: Asthma Quality of Life Questionnaire; RV: residual volume; CT: computed tomography; FVC: forced vital capacity; 6MWT: 6-min walk test; SGRQ: St George's Respiratory Questionnaire; mMRC: modified Medical Research Council dyspnoea score; CAT: COPD Assessment Test.

reduction in ICS daily dose with stable pre-bronchodilator FEV₁ values. Computed tomography (CT) scan performed at year 5 (n=93 subjects) showed no abnormalities attributable to bronchial thermoplasty.

A post-US Food and Drug Administration (FDA) approval study conducted in the USA (the PAS2 study) included 190 patients showing a decrease in the number of severe exacerbations, emergency department visits and hospitalisation at 3 years [21].

Long-term analysis of bronchial thermoplasty impact beyond 1 year relies on data from two RCTs and one real-life study. These results suggest long-term safety and persistence of benefits.

Current recommendations

International recommendations do not recommend bronchial thermoplasty as routine management of severe asthma. The European Respiratory Society/American Thoracic Society guidelines of severe asthma management [22] do recommend that bronchial thermoplasty is performed in adults with severe asthma only in the context of an Institutional Review Board-approved independent systematic registry or a clinical study. The 2020 Global Initiative for Asthma guidelines [23] specify that bronchial thermoplasty is a potential treatment option at Step 5 in some countries for adult patients whose asthma remains uncontrolled despite optimisation of asthma therapy and referral to a severe asthma specialty centre (Evidence B), and should be performed in adults with severe asthma only in the context of an independent Institutional Review Board-approved systematic registry or a clinical study. Both international guidelines base these recommendations on the limited evidence for bronchial thermoplasty efficacy and long-term safety in severe asthma.

Emphysema

The aim of bronchoscopic techniques in emphysema is to reduce hyperinflation. The three main techniques with available robust RCT results are endobronchial valves, coils and thermal vapor ablation.

Endobronchial valves

Endobronchial one-way valves are placed through fiberoptic bronchoscopy in segmental bronchi in a targeted lobe. Valves allow expiratory flow of air while blocking inspiratory flow in the targeted lobe, therefore resulting in the reduction of lobar volume which can eventually lead to full lobar collapse. Among several endobronchial valves developed so far, two valves only have been assessed in RCTs: the Zephyr one-way endobronchial valve (EBV) (PulmonX, Redwood City, CA, USA) and the Spiration valve system (SVS) (Olympus, Redmond, WA, USA) previously known as an intra-bronchial valve. Early nonrandomised studies and *post hoc* analyses from RCTs clearly indicated that both collateral ventilation and nonoptimal placement of the valves with incomplete treatment of a targeted lobe were associated with poor efficacy results. These results lead to selecting patients based on the absence of collateral ventilation assessed by CT scan and/or endobronchial measurements using the Chartis system (PulmonX). In this review, we will focus on RCTs with inclusion criteria including the absence of collateral ventilation and with complete lobar treatment by valves.

Levels of evidence

Seven RCTs selecting patients with no or little collateral ventilation and complete lobar treatment have been conducted (table 1). Five RCTs used the EBV system, and two used the SVS system. All these RCTs used unilateral occlusion of a targeted lobe by valves.

EBV system

The BeLieVeR-HIFI study is a single-centre sham-controlled study conducted in the UK that included 50 patients (EBV: n=25; sham: n=25) [9]. The main inclusion criteria were $FEV_1 < 50\%$, residual volume (RV) $> 150\%$, 6-min walk test (6MWT) < 450 m, modified Medical Research Council (mMRC) dyspnoea score ≥ 3 , heterogeneous emphysema and intact interlobar fissure based on CT scan assessment. The primary end-point of FEV_1 change at 3 months, was significantly higher in the EBV group than in the sham group (table 1). Among the four patients in the EBV group with collateral ventilation detected using the Chartis system despite intact fissure diagnosed by CT scan, none had an improvement in FEV_1 , highlighting the importance of absence of collateral ventilation for EBV effectiveness. Secondary end-points demonstrated a significant improvement in the 6MWT, but no significant changes for the mMRC scale, St George's Respiratory Questionnaire (SGRQ) score, or RV at 3 months. Follow-up data, including patients treated by EBV from the sham group (n=12) and the initial EBV group with no collateral ventilation based on Chartis assessment reported much better results with an improvement from baseline in FEV_1 , RV, 6MWT and SGRQ score [24].

The STELVIO study is a single-centre randomised study conducted in the Netherlands, including 68 patients (EBV: n=34; usual care: n=34) [10]. The main inclusion criteria were $FEV_1 < 60\%$, RV $> 150\%$, heterogeneous emphysema, and absence of collateral ventilation assessed by Chartis. Significant improvement was found at 6 months for FEV_1 , forced vital capacity (FVC) and 6MWT in the EBV group compared to the usual care group. Results at 1 year for the EBV group and the control group who crossed over were reported for 40 out of 64 patients treated by EBV [25]. Significant improvements from baseline were reported for FEV_1 , RV, 6MWT and the SGRQ score. Two deaths occurred during the 1-year follow-up period.

The IMPACT study is a multicentre study conducted in Germany, the Netherlands and Austria, including 93 patients (EBV: n=43; usual care: n=50) with inclusion criteria including $15\% < FEV_1 < 45\%$, RV $> 200\%$, homogeneous emphysema, and absence of collateral ventilation assessed by Chartis [11]. Significant improvement was found for FEV_1 change at 3 months relative to baseline in the EBV group (+13.7% *versus* -3.2%). Secondary end-points at 3 months also demonstrated improvement in the EBV group compared to the control group for RV, SGRQ score and 6MWT.

The TRANSFORM study is a multicentre study conducted in the UK, Netherlands, Belgium, Sweden, France and Germany, including 97 patients (EBV: n=65; control: n=32). The main inclusion criteria were $15\% < FEV_1 < 45\%$, RV $> 180\%$, heterogeneous emphysema and absence of collateral ventilation assessed by Chartis [12]. The primary end-point was the percentage of subjects with an improvement of $FEV_1 \geq 12\%$ in the EBV group compared to control at 3 months, which was achieved by 55.4% in the EBV group and 6.5% in the control group. At 6 months, improvements were maintained in the EBV group for FEV_1 . Between-group differences at 6 months were significant for RV, 6MWT and SGRQ.

The LIBERATE study is a multicentre study conducted in the USA, Brazil, UK, and the Netherlands, including 190 patients (EBV: n=128; usual care: n=62). The main inclusion criteria were $15\% < FEV_1 < 45\%$, RV $> 175\%$, heterogeneous emphysema and absence of collateral ventilation assessed by Chartis [15]. The primary end-point was the percentage of patients with a $FEV_1 \geq 15\%$ from baseline at 12 months, which

was achieved in 47.7% in the EBV group and 16.8% in the control group. Secondary end-points at 12 months showed a significant between-group difference for FEV₁, RV, 6MWT and the SGRQ score.

All five RCTs using the EBV system reported pneumothorax as a major adverse event, occurring from 8% to 33.2% in the EBV groups [9–13] and most frequently in the first 30–45 days following treatment [12, 13]. The TRANSFORM study precisely described the management of pneumothorax: intervention and/or hospitalisation in 14 out of 19 subjects, observation in eight cases, placement of chest drain in 11 cases, and surgery in one case [12]. Pneumothorax-related deaths were reported in three cases in the LIBERATE study and one case in the TRANSFORM study [12, 13]. Overall, valve removal or replacement was reported in 8–32% of cases [9–13].

SVS system

The REACH study is a multicentre study conducted in China including 99 patients (SVS: n=66; usual care: n=33) [14]. The main inclusion criteria were FEV₁ ≤45%, RV ≥150%, heterogeneous emphysema, and intact interlobar fissure assessed visually by CT scan. Changes in FEV₁ at 3 months were higher in the SVS group compared to the control group (table 1).

The EMPROVE study is a multicentre study conducted in the USA and Canada, including 172 patients (SVS: n=113; usual care: n=59) [15]. The main inclusion criteria were FEV₁ ≤45%, RV ≥150%, heterogeneous emphysema, and intact interlobar fissure assessed visually by CT scan (≥90% complete fissure with no segmental vessels crossing from adjacent lobes). The primary end-point analysis at 6 months showed a higher FEV₁ in the SVS group when compared with the control group. This difference in FEV₁ was maintained at 12 months. At 6 months, the SVS group exhibited significant improvements in RV and SGRQ score but not for the 6MWT.

The rate of pneumothorax at 6 months in the SVS groups was 7.6% in the REACH study, and 25.7% in the EMPROVE study, including 14.2% serious pneumothorax defined as requiring surgical intervention or prolonged air leak for >7 days [14, 15]. As described with the EBV system, most of the pneumothorax occurred early after procedure: 66% within 3 days after SVS procedure [15].

Overall, seven RCTs assessing valves (five for EBV, two for SVS) demonstrated clinically significant improvements at 3, 6 or 12 months with an acceptable safety profile. Pneumothorax is a frequent adverse event requiring close monitoring of patients for at least 3 days post-procedure by experienced teams able to rapidly treat pneumothorax. In some patients, additional procedures for replacement or removal of valves are needed.

Regarding these seven RCTs, only one study included a sham group for control, with no effect on the primary end-point based on percent change in FEV₁ at 3 months. The inclusion criteria were relatively homogeneous, selecting patients with high hyperinflation and none-to-little collateral ventilation. The primary end-points were somewhat heterogeneous regarding the time-points with assessments at 3 months for four RCTs, 6 months for two RCTs and 12 months for one RCT. 3-month time-point results have to be considered cautiously in a chronic respiratory disease such as emphysema. FEV₁ was included in all RCTs as the primary end-point, alone in six RCTs and in combination with FVC and 6MWT in one study. FEV₁ was analysed as difference in percent or absolute value changes between groups, or using cut-off of 12% or 15%.

The GRADE level of evidence for valves from these seven RCTs is high with a low risk of bias, a low risk of imprecision, consistency in efficacy results, no evident indirectness, and no known publication bias.

Long-term follow-up results

Despite many RCTs assessing valves in severe emphysema, data beyond 1 year are sparse.

A retrospective study assessed 10-year survival in 19 patients treated by EBV comparing patients with or without atelectasis assessed by CT scan at 1 month post-procedure [26]. In the atelectasis group, two (40%) of five patients were still alive at 10 years compared with two (14%) out of 14 patients in the group without atelectasis.

A study assessed 38 patients treated by EBV in clinical trials in Groningen (the Netherlands) who were invited for voluntary annual visit [27]. Data were available for 27 patients at 2 years and 22 patients at 3 years. At 2 years, significant improvement compared to baseline was found for RV, mMRC scale and SGRQ score. At 3 years, only the mMRC dyspnoea scale remained statistically improved. The rate of pneumothorax was 6% during the first year, which was lower than that reported in RCTs probably because of a selection bias excluding patients with early valve removal. Of note, no other pneumothorax occurred during the second and third year of follow-up.

A retrospective real-life study assessed the outcome after EBV treatment in 256 patients treated at Heidelberg (Germany) [28]. 2- and 3-year follow-up visits were available in 100 and 66 patients, respectively. At 2 years, significant improvement was shown for RV (-0.35 L) and total lung capacity (-0.38 L), but not for FEV₁ and 6MWT. At 3 years, only mMRC scale change (-0.5) was statistically improved. Patients with complete lobar atelectasis exhibited superior results at 3 years for FEV₁, RV and 6MWT. Regarding safety, pneumothorax occurred in 22% of the patients, with 86% of these patients requiring chest tube insertion, and 41% required valve removal. During the 3-year follow-up, all valves were permanently removed in 24.6% of the patients.

Current recommendations

The 2020 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report indicates that valves can be considered when available in both heterogeneous and homogeneous emphysema, with no collateral ventilation (Evidence A) [29]. Recommendations from an international expert panel updated in 2019 stated that valves reached the evidence level to be used outside clinical trials in heterogeneous or homogeneous emphysema without collateral ventilation [30]. The US FDA approved valves in routine clinical practise in 2019. Valves are also approved in many countries in Europe and Asia.

Coils

Endobronchial shape-memory nitinol coils (BTG/PneumRx, Mountain View, CA, USA) are devices inserted into subsegmental bronchi to induce lung volume reduction and enhance lung recoil. Under general anaesthesia, approximately 10 coils (sizes 100, 125 or 150 mm) are placed in a targeted lobe through a catheter inserted in a bronchoscope with deployment guided by fluoroscopy. A contralateral treatment is usually performed 1 to 3 months after the first procedure.

Levels of evidence

Three RCTs assessed endobronchial coils in severe emphysema (table 1).

The RESET study is a multicentre study conducted in the UK which included 47 patients allocated to coil treatment (n=23) or usual care (n=24) [16]. The main inclusion criteria were a post-bronchodilator FEV₁ $\leq 45\%$, mMRC scale ≥ 2 , and either homogeneous or heterogeneous emphysema. A significant improvement was noted for SGRQ score, the primary end-point, at 90 days in the coil group compared to the control group. Secondary end-points analyses also showed significant between-group differences for FEV₁, RV and the 6MWT. 12-month follow-up results from the RESET study, including both the cross-over and initial coil groups (n=45), showed an improvement from baseline for the SGRQ score, FEV₁ and the 6MWT.

The REVOLENS study is an independent multicentre study conducted in France that included 100 patients (coil group: n=50; usual care: n=50) [17]. The main inclusion criteria were a post-bronchodilator FEV₁ $< 50\%$ and RV $\geq 220\%$, and formal pulmonary rehabilitation within the previous 12 months. The population exhibited very severe airflow limitation and hyperinflation, and mainly homogeneous emphysema. The primary end-point, which was the improvement of at least 54 m in the 6MWT at 6 months compared to baseline was achieved. Mean between-group changes at 12 months were significant for FEV₁ and SGRQ score.

The RENEW study is a multicentre study conducted in the USA and Europe, which included 315 patients randomised into the coil group (n=157) or usual care group (n=158) [18]. The main inclusion criteria were a post-bronchodilator FEV₁ $< 45\%$ and RV $\geq 225\%$ which was lowered to $\geq 175\%$ after enrolment of 169 patients. Overall, the population exhibited severe hyperinflation and predominant homogeneous emphysema. The primary end-point which was the difference in the 6MWT between baseline and 12 months in both groups was achieved. Between-group differences at 12 months for effectiveness outcomes were significant for FEV₁ and SGRQ. A *post hoc* analysis of the RENEW study identified that significant hyperinflation (RV $> 200\%$) and CT analyses including a quantitative assessment to identify optimal lobar treatment with $> 20\%$ low attenuation area and a visual CT assessment to verify the absence of airway disease were predictors of response to endobronchial coil [31].

Regarding safety, the two main serious adverse events reported were pneumonia and pneumothorax. In the RESET study, two pneumothoraces (5%) occurred in the coil group, and none in the usual care group. No between-group difference was detected regarding serious adverse events. In the REVOLENS study, pneumonia was more frequent in the coil group (18% *versus* 4%), whereas pneumothorax was not statistically more frequent (6% *versus* 2%) within 12 months. In the RENEW study, major complications were also more frequent in the coil group including pneumonia (20% *versus* 4.5%) and pneumothorax (9.7% *versus* 0.6%). The majority of pneumothoraces occurred during the first day post-coil treatment. Pneumonia occurred more frequently during the first month post-procedure.

Overall, the three RCTs assessing coils showed similar results with significant improvement in hyperinflation, exercise tolerance and quality of life, with an acceptable safety profile. The risks of pneumonia and pneumothorax require pre-specified therapeutic management plans.

One limitation of the three RCTs is that no RCT included a sham group for control. The inclusion criteria in the three RCTs were relatively similar, selecting patients with severe airflow obstruction, homogeneous and heterogeneous emphysema, and severe hyperinflation. The primary end-points were somewhat heterogeneous regarding the time points with assessments at 3, 6 and 12 months. Results from short-time end-points have to be considered cautiously in emphysema. Primary end-points included quality of life in one study, and 6MWT results in two RCTs.

The GRADE level of evidence from the three RCTs is moderate with a low risk of bias, a low risk of imprecision, consistency in the efficacy results but limited to three RCTs, no evident indirectness, and no known publication bias.

Long-term follow-up results

Results beyond 1 year are available from two RCTs [32, 33] and one nonrandomised study [27].

A retrospective secondary analysis of the RESET study analysed 5-year survival after coil treatment [33]. The aim of this study was to assess 5-year overall and transplant-free survivals of patients treated by coils in the RESET study. The 5-year overall survival was 50.6%, and the 5-year transplant-free survival was 46.7%. Volume reduction responders at 3 months defined by a RV reduction of at least 10% had a higher 5-year transplant-free survival than nonresponders.

2-year prospective follow-up data from 50 patients treated in the coil group in the REVOLENS showed sustained improvement from baseline in RV and SGRQ score, whereas changes in FEV₁ and 6MWT were not significant [32]. Serious adverse events decreased after 1 year, with no unanticipated events occurring. No late pneumothorax or haemoptysis events were reported.

Data from 35 patients treated by coils in nonrandomised studies and who were invited for a voluntary annual visit at 1 (n=35), 2 (n=27) and 3 years (n=22) have been reported [27]. A significant improvement from baseline was found for RV, mMRC scale and SGRQ score at 2 years, whereas the mMRC scale only was significantly improved at 3 years. The rate of responders at 3 years was 59% for the SGRQ score (≤ 4 points), 38% for FEV₁ ($\geq 10\%$), 19% for RV (≤ 400 m), and 40% for 6MWT (≥ 26 m). No late pneumothorax, coil migration or unexpected adverse event was reported beyond 1 year.

Current recommendations

The 2020 GOLD report indicates that coil treatment can be considered when available in both heterogeneous and homogeneous emphysema, with or without collateral ventilation (Evidence B) [29]. Recommendations from an international expert panel updated in 2019 recommended to consider coils in patients with heterogeneous or homogeneous emphysema with or without collateral ventilation, and with significant emphysema (low attenuation area $>20\%$ at 950 HU), hyperinflation (RV $>225\%$ and RV/total lung capacity >0.58), and no signs of significant airway wall thickening, bronchiectasis, or clinically significant chronic bronchitis [30].

Thermal vapor ablation

Thermal vapor ablation (TVA) (Uptake Medical Corporation, Seattle, WA, USA) is a bronchoscopic technique using instillation of heated water in the most destroyed part of upper lobes in a procedure usually performed under general anaesthesia or deep sedation [34]. Heated water locally induces an inflammatory response leading to parenchymal fibrosis and subsequent lung volume reduction. TVA has been assessed in one RCT.

Levels of evidence

The STEP-UP study is a multicentre study conducted in Germany, Austria, UK, Ireland and Australia, including 70 patients (TVA: n=46; usual care: n=24) [19]. The coprimary end-points were significantly improved in the TVA group compared to the control group for FEV₁ and SGRQ scores at 6 months. Both FEV₁ and SGRQ score remained significantly improved at 12 months, whereas RV and the 6MWT were not significantly different between the two groups [35]. A *post hoc* analysis of the STEP-UP study analysed the results for patients with collateral ventilation (78% of the patients treated by TVA), demonstrating as expected a significant improvement for FEV₁ and SGRQ in this population [36]. These results highlight that TVA effectiveness is independent from collateral ventilation.

Regarding safety, COPD exacerbation occurred in 24% of the patients in the TVA group compared to 4% in the usual care group at 6 months [19]. One death was related to a COPD exacerbation occurring at day

84, and was adjudicated as possibly related to TVA. No pneumothorax occurred within 30 days of treatment. Interestingly, the rate of serious adverse events was similar between both groups for the period 90–360 days [35].

The level of evidence for TVA relies on one RCT only, justifying conducting additional RCT in larger population to confirm these results.

The GRADE level of evidence for TVA relying on one RCT is low with a moderate risk of bias, a moderate risk of imprecision, absence of possibility to assess consistency because of available data from one RCT only, no evident indirectness, and no known publication bias.

Long-term follow-up results

No data beyond 1 year are currently available for TVA.

Current recommendations

The 2020 GOLD report indicates that TVA can be considered when available in heterogeneous emphysema (upper predominant), with or without collateral ventilation (Evidence B) [29]. Recommendations from an international expert panel updated in 2019 recommended considering TVA in upper lobe predominant heterogeneous emphysema only in clinical trials [30].

Sealant

The emphysematous lung sealant system (ELS) (PulmonX) employs a synthetic polymer delivered by fiberoptic bronchoscopy in upper lobe subsegments to induce remodelling and scar formation, therefore promoting atelectasis and reducing lung hyperinflation. Early nonrandomised studies showed promising results [37, 38] leading to the ASPIRE RCT [39]. Unfortunately, this RCT was terminated early for business reasons with 95 patients randomised out of 300 patients initially planned, and the primary 12-month end-point was then not assessed. Results at 3 months (57 patients) and 6 months (34 patients) suggested improvements in the ELS group in lung function, dyspnoea and quality of life [39]. Regarding safety, adverse events requiring hospitalisation were 2.5-fold more frequent in the ELS group compared to controls, including pulmonary acute infiltratory response, COPD exacerbation, pneumonia and pneumothorax. Two deaths occurred in the ELS group.

The GRADE level of evidence for ELS is very low with a high risk of bias, a high risk of imprecision, an absence of possibility to assess consistency because of available data from one incomplete RCT only, indirectness, and no known publication bias.

Because of early termination of the only RCT, no definite conclusion can be drawn regarding efficacy and safety of ELS, thus requiring additional well-conducted RCTs.

COPD

Targeted lung denervation (TLD) is a novel bronchoscopic treatment aimed at attenuating parasympathetic overactivity in COPD by disrupting the peribronchial vagal innervation of the lung. Radiofrequency energy is delivered through a catheter with activation of the electrode in up to four positions in both main bronchi. The procedure is performed under general anaesthesia with bronchoscopic and fluoroscopic visualisation.

Levels of evidence

The first studies of TLD conducted in COPD assessed its feasibility and safety, and allowed optimal dosing and prevention and management of adverse events to be defined [40–42].

The AIRFLOW-2 is a multicentre sham bronchoscopy RCT conducted in symptomatic COPD patients (mMRC ≥ 2 or COPD assessment test ≥ 10) with FEV₁ 30–60% predicted [20]. 82 patients were randomised to the TLD group with both lungs treated in a single procedure (n=41) or to the sham group (n=41). The primary end-point was safety. The TLD group experienced fewer respiratory adverse events between 3 and 6.5 months post-TLD than the sham group. Secondary analyses showed that the rate of respiratory adverse events between 0 and 12.5 months post-TLD were not different between both groups, whereas the rate of COPD exacerbation requiring hospitalisation between 0 and 12.5 months post-TLD was lower in the TLD group. The overall number of serious adverse events was similar between both groups; however, there was a trend for increased gastrointestinal effects in the TLD group. Of note, there was no statistically significant difference in symptoms and lung function tests between groups over the 12.5 months of follow-up.

So far, results from only one RCT evaluating TLD in COPD have been published. The design of this RCT including a sham group and the results suggesting a reduction of respiratory events including COPD

exacerbation requiring hospitalisation are interesting, but require additional RCTs from a larger population to confirm these findings. The AIRFLOW-3 study is an ongoing multicentre sham bronchoscopy RCT which should allow the ability to determine the efficacy and safety of TLD in COPD [43].

Because of the design of the only one RCT with a primary end-point for safety, it is difficult to assess the GRADE for TLD, thus requiring additional studies with efficacy primary end-points.

Long-term follow-up results

Data beyond 1 year are available from one prospective study including 15 patients treated on both lungs by TLD in a single procedure (n=13) or two procedures (n=2) [41]. Follow-up data are available for 15 patients at 1 year, 10 patients at 2 years, and nine patients at 3 years. The primary safety end-point was freedom from sustained worsening of COPD attributable to TLD up to 1 year, which was found in all the patients. Follow-up until 3 years was conducted in patients who consented for longer follow-up. Lung function and exercise capacity assessments conducted at 2 and 3 years post-TLD demonstrated similar beneficial effects of TLD without bronchodilators when compared with long-acting anticholinergic therapy.

12 serious adverse events including five respiratory events were reported through 3 years of follow-up, with no events related to TLD.

Current recommendations

The level of evidence is currently too low with available data from only one RCT to include TLD in therapeutic guidelines for COPD management. Additional RCTs are needed to confirm promising results, especially regarding the impact on severe COPD exacerbation.

Conclusion

The levels of evidence for interventional bronchoscopic techniques in asthma, COPD and emphysema largely improved in the past 15 years with many available RCTs results. To translate RCT results into clinical practice, these bronchoscopic techniques have to be considered in a multidisciplinary approach including precise assessment of asthma, COPD or emphysema phenotypes, comorbidities, as well as optimisation of medical management following international guidelines. Rigorous selection of the patients, experience and training in bronchoscopic procedures and management of potential adverse events are very important points to consider [44]. The risk benefit ratio has to be clearly discussed with the patients including potential efficacy, safety issues, and patient's preference. Data regarding long-term follow-up results beyond 1 year are currently sparse, especially in emphysema and COPD. The place of these bronchoscopic techniques in the global management of asthma, COPD and emphysema remains to be evaluated in clinical practice in real-life studies. Inclusion of patients in clinical studies or registries should be encouraged in order to obtain a higher level of evidence and long-term efficacy and safety data for each bronchoscopic technique.

Conflict of interest: J.M. Perotin has nothing to disclose. M. Dewolf has nothing to disclose. C. Launois has nothing to disclose. V. Dormoy has nothing to disclose. G. Deslee reports personal fees from BTG/PneumRx and Nuaira, during the conduct of the study; personal fees from Chiesi, Boehringer Ingelheim, AstraZeneca and Novartis, outside the submitted work.

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