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Lung volume reduction for emphysema

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Advanced emphysema is a lung disease in which alveolar capillary units are destroyed and supporting tissue is lost. The combined effect of reduced gas exchange and changes in airway dynamics impairs expiratory airflow and leads to progressive air trapping. Pharmacological therapies have limited effects. Surgical resection of the most destroyed sections of the lung can improve pulmonary function and exercise capacity but its benefit is tempered by significant morbidity. This issue stimulated a search for novel approaches to lung volume reduction. Alternative minimally invasive approaches using bronchoscopic techniques including valves, coils, vapour thermal ablation, and sclerosant agents have been at the forefront of these developments. Insertion of endobronchial valves in selected patients could have benefits that are comparable with lung volume reduction surgery. Endobronchial coils might have a role in the treatment of patients with emphysema with severe hyperinflation and less parenchymal destruction. Use of vapour thermal energy or a sclerosant might allow focal treatment but the unpredictability of the inflammatory response limits their current use. In this Review, we aim to summarise clinical trial evidence on lung volume reduction and provide guidance on patient selection for available therapies.

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Introduction

Emphysema is a destructive process of the lung parenchyma characterised by the permanent enlargement of air spaces distal to the terminal bronchioles. It is principally induced by cigarette smoking, but is also associated with inhalation of fumes and dust. As inferred from its Greek name (*emphusēma*, a swelling up) the pathological process leads to hyperinflation.[1] Appropriate treatment with a holistic approach should include smoking cessation, pulmonary rehabilitation, optimal nutrition, and vaccination against influenza and pneumococcal infections. Pharmacological therapies consisting of both short-acting and long-acting β_2 agonists and anticholinergic agents are almost universally administered in developed countries but response to these therapies is limited in patients with a predominant emphysema phenotype.[2] Innovative therapeutic strategies that induce lung volume reduction have been developed in the past decade, including novel trial designs. The results indicate that precise emphysema phenotyping is necessary and that it provides personalised therapies for patients with emphysema. The gold standard approach necessitates a multidisciplinary team so that patients receive comprehensive treatment from rehabilitation through to a lung volume reduction intervention that is appropriate for the patient.

Surgical lung volume reduction

Lung volume reduction surgery (LVRS) was initially introduced in 1957 by Brantigan and Mueller, who described it as a reduction pneumoplasty consisting of an open thoracotomy followed by resection of the most emphysematous parts of the lung.[3] The principle was that removal of these overcompliant areas of lung would reduce air trapping and facilitate ventilation of the relatively healthy areas of lung tissue, which in turn would reduce ventilation and perfusion mismatch and also improve diaphragm function (figure 1). In 1999, Criner and colleagues[4] reported a randomised study comparing LVRS with pulmonary rehabilitation in 19 patients and pulmonary rehabilitation alone in 18 patients with severe diffuse bullous emphysema. Statistically significant improvements in pulmonary function parameters were noted at 3 months in the LVRS group. However, 6 min walk distance (6MWD) did not significantly improve in either group after the initial intervention. Another randomised study[5] in the UK reported improvements in the median shuttle walk distance at 6 months in patients with severe diffuse emphysema but without large focal bulla who received LVRS compared with those who only received medical therapy (increased by 50 m for 24 patients in the LVRS group and decreased by 20 m for 24 patients who continued medical treatment, p=0·02). Medical therapy for emphysema would consist of immunisation, inhaled beta agonists, anti-muscarinic drugs, and selected patients receive corticosteroids. Pulmonary rehabilitation is considered a standard part of medical

Key messages

- Treatment options for patients with severe symptomatic emphysema and hyperinflation are limited and lung volume reduction and lung transplantation should be considered
- All emphysema patients should undergo pulmonary rehabilitation and should be on optimal medical treatment
- Lung volume reduction surgery remains an effective option in selected patients with either paraseptal or heterogeneous emphysema
- Treatment decisions should be made by a multidisciplinary team in conjunction with patients
- Endobronchial valves should be considered for patients with heterogeneous disease with intact lobar fissures or absent collateral ventilation
- Lung volume reduction coils might be an option in patients with severe hyperinflation and homogeneous disease and for patients with heterogeneous disease in the presence of collateral ventilation

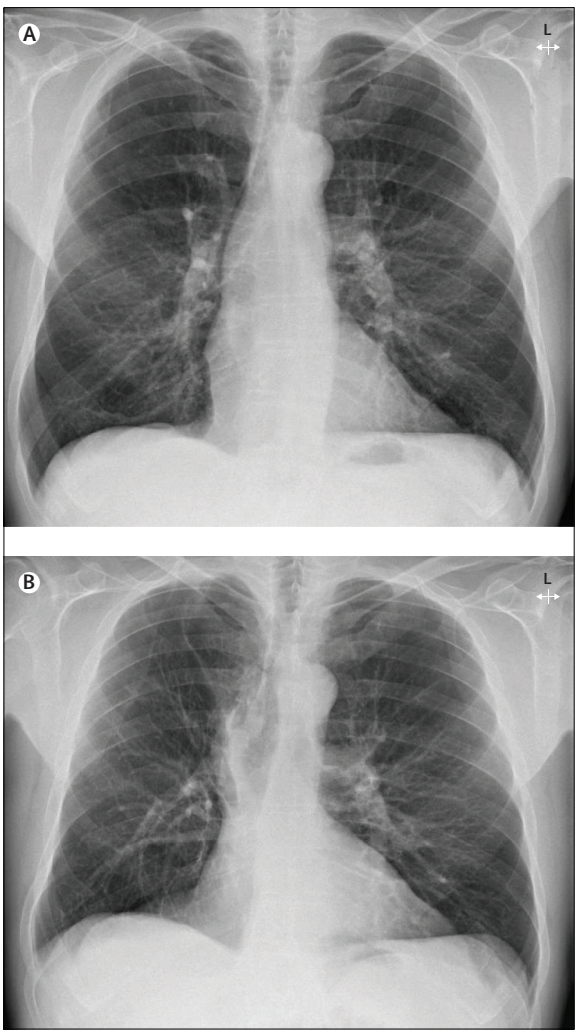

***Figure 1*: Radiographs of lung volume reduction surgery**
(A) Chest radiograph before lung volume reduction surgery. (B) Chest radiograph 3 months after lung volume reduction surgery using an anatomical resection technique of the right upper lobe and middle lobe.

therapy in the clinical trials that have been performed in the last decade. Except where stated otherwise, patients are randomised to intervention plus optimal medical therapy versus medical therapy alone. A similar study[6] enrolled patients who had severe diffuse emphysema but did not further select according to the distribution of the disease; the results indicated significant improvements in quality of life but significantly higher mortality in patients treated with LVRS (28 patients) compared with medical therapy alone (27 patients). In another study,[7] patients with severe diffuse emphysema were randomly assigned to either LVRS with continued physical training for 3 months, or to continued physical training. Significant improvements in pulmonary function (forced expiratory volume in one second [FEV_1]) and quality of life (St George's Respiratory Questionnaire [SGRQ], mean difference at 1 year –14·7, 95% CI –9·8 to –19·7). There were six in-hospital deaths (12%) after surgery versus two during follow-up in the treatment as usual group.

The National Emphysema Treatment Trial (NETT)[8] was the largest randomised trial to evaluate LVRS (608 patients) versus medical therapy (610 patients). Overall mortality was similar in the two groups. However, 90-day mortality was higher in the LVRS group (7·9%, 95% CI 5·9–10·3) compared with the medical group (1·3%, CI 0·6–2·6; p<0·001). The trial identified a high responder group who responded most to LVRS (upper lobe-predominant emphysema with low baseline exercise capacity), and also a high-risk group with an increased mortality (patients with FEV_1<20% and either homogeneous emphysema or a predicted diffusion capacity for carbon monoxide of <20%). Early reports of increased mortality with LVRS seem to have influenced both the medical community and patients. Around 100 LVRS procedures are performed each year in the UK and an even smaller number of procedures have been performed in the USA since NETT—Medicare reported 93 LVRS procedures in 2011, 65 in 2012, and 42 in 2013.[9] The main contributor to mortality observed after LVRS is early in-hospital mortality. To put this into perspective, 5-year follow-up shows a significant survival benefit for patients in the NETT best responder cohort patients (patients with upper lobe predominant disease and low exercise tolerance at baseline).[10] Since the publication of the NETT study, and because of the serious specific mortality associated with LRVS, substantial developments have been made that have led to greater use of video-assisted thoracoscopic approaches and unilateral treatment for emphysema. However, prolonged air leakage remains a problem in LVRS, leading some centres to use a non-resectional approach.[11] This technique involves use of adapted staples that effectively separate two regions of the lung without cutting through, with the emphysematous parts of a lobe left folded in place. Several centres still offer LVRS and 90-day mortality in some surgical centres has been reported as less than 1% in recent years.[12] Nevertheless, patients tend to opt for less invasive and potentially reversible options.

Endobronchial valves

Endobronchial lung volume reduction using one-way endobronchial valves is designed to mimic the physiological effects of LVRS by unilaterally excluding the most diseased lobe of the lung. Valves are placed in all segmental bronchi of the target lobe and the resulting deflation and absorption atelectasis reduces hyperinflation (figure 2).[13] However, lobar exclusion cannot be achieved in all patients because of the extensive interlobar collaterals present in the emphysematous lung. Insertion of endobronchial valves is the only endoscopic technique discussed in this Review that is completely reversible.

The most common complication is pneumothorax after the procedure, but this event can also ultimately lead to a clinical response for the patient.[14] Clinical benefit with endobronchial valves is more likely when lobar atelectasis occurs, which in turn leads to a shift in the position of the ipsilateral lobe. The presence of adhesions might lead to pneumothorax. Hence, some authors believe that a pneumothorax is a surrogate marker of response and probable clinical benefit.

The Endobronchial Valve for Emphysema Palliation Trial (VENT) study[15,16] was a multicentre 2:1 randomised study comparing the safety and efficacy of unilateral endobronchial valves versus standard medical care in patients with heterogeneous emphysema. The co-primary endpoints for efficacy were percentage change in FEV_1 and 6MWD at 6 months after randomisation. The results of patients enrolled in the USA (n=321) and in Europe (n=171) were analysed and reported separately.[15,16] In patients enrolled in the USA, the results at 6 months showed a between-group difference in favour of endobronchial valve placement of 6·8% in FEV_1 (p=0·005), 19·1 m in 6MWD (p=0·02), and −3·4 points on the SGRQ (p=0·04).[15] In patients enrolled in Europe, the results at 6 months showed a between-group difference of 6·5% in FEV_1 (p=0·067), 5 m in 6MWD (p=0·696), and −4·7 points on the SGRQ (p=0·047);[16] however, the size of the European study lacked the power to support a robust statistical analysis for the primary and secondary endpoints. Post-hoc analyses showed that a complete fissure was associated with a better response in FEV_1. Similarly, patients with confirmed correct valve placement on high resolution CT (HRCT) had greater improvements in both FEV_1 and 6MWD, compared with the control group and those with confirmed incorrect valve replacement. High heterogeneity in the degree or severity of emphysema (evaluated at 950 Hounsfield units within an individual patient's CT scan) was associated with a greater improvement in FEV_1 and 6MWD in US patients, but not in European patients. At 90 days in the US cohort, the rate of chronic obstructive pulmonary disease (COPD) exacerbations requiring hospitalisation (7·9% *vs* 1·1%, p=0·03) and haemoptysis (6·1% *vs* 0%, p=0·01) were increased in the endobronchial valve group. By contrast, the rates of COPD exacerbations requiring hospitalisation and haemoptysis at 3 months were not statistically increased in the endobronchial valve group in the European cohort. The rates of pneumonia distal to valves were 4·2% in US patients and 6·3% in European patients at 12 months. Pneumothorax within 3 months after valve placement occurred in 4·2% of US patients and 4·5% of European patients. Valve migration, aspiration or expectoration occurred in 4·7% of US patients. Overall, the VENT study showed that endobronchial valves induced a modest improvement in lung function, exercise tolerance, and quality of life, and had an acceptable safety profile. More importantly, this study strongly suggested that both fissure integrity and technically perfect occlusion of the target lobe were key to obtaining a clinically significant response to valve treatment. On the basis of these results, assessment of

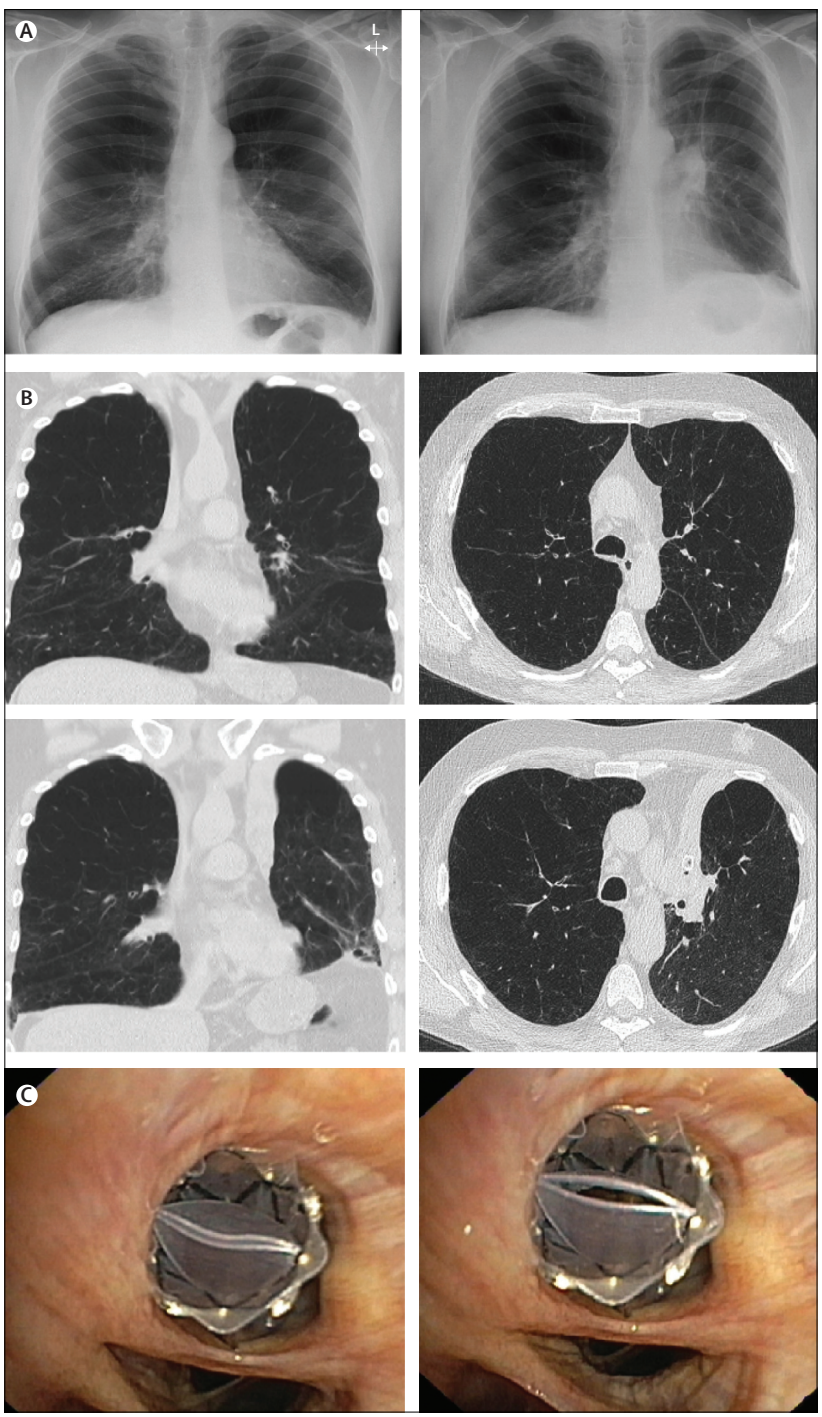

Figure 2: **Radiographs of endobronchial valves**
(A) Chest radiograph before (left) and after (right) insertion of endobronchial valves. (B) CT scan before (top) and after (below) insertion of endobronchial valves with atelectasis. (C) Bronchoscopic image of the valves closed (left) during inspiration and open (right) during expiration.

collateral ventilation is essential for the selection of responders to endobronchial valves. In addition to assessment of HRCT scans, the bronchoscopic Chartis Pulmonary Assessment System was developed for in-vivo measurements of collateral ventilation. A non-randomised multicentre prospective study[17] of 96 patients showed its safety and effectiveness for prediction of the response to endobronchial valve treatment.

The BeLieVeR-HIFi[18] and STELVIO[19] studies were small single-centre studies that provide encouraging data supporting the use of endobronchial valves in carefully selected patients with emphysema. The BeLieVeR-HIFi study[18] is the only randomised full sham bronchoscopy controlled study to use endobronchial valves. This study randomly assigned patients with emphysema and hyperinflation with both heterogeneous disease and fissure integrity of more than 90% on HRCT. All patients had a Chartis assessment but proceeded to the assigned intervention irrespective of these findings, thus providing information about the added benefit or value of performing Chartis to assessment of fissure integrity on CT scans: 50 patients were randomly assigned equally to endobronchial valve insertion with usual medical care (n=25) or a sham procedure and usual medical care (n=25). At baseline, the patients had severe disease with a mean FEV_1 of 31·7% of predicted, residual volumes of 232% of predicted, an SGRQ total score of 71·2, and a 6MWD of 338 m. 23 episodes in 16 patients in the treatment group were described as exacerbations and 22 episodes in 20 patients in the sham group were described as exacerbations. Two episodes of pneumonia, two pneumothoraxes, and two deaths occurred in the treatment group. The primary endpoint of the study (FEV_1) was improved by a mean of 24·8% (95% CI 8·0–41·5; median change 8·8%) in the intervention group compared with 3·9% (CI 0·7–7·1; 2·9%) in the sham group. However, in this study four patients in the treatment group had collateral ventilation present on Chartis assessment and a further four had an indeterminate Chartis assessment. Exclusion of these patients with collateral ventilation significantly improved the responder rate for FEV_1, 6MWD, and exercise endurance time.[18]

The STELVIO trial[19] investigated the efficacy and safety of placement of endobronchial valves for patients with severe emphysema with intact fissures who had an absence of collateral ventilation as measured by the Chartis system. The STELVIO trial protocol allowed re-evaluation of any non-responders, which created a further opportunity to optimise the procedure (ie, repositioning of the valve or valves) in advance of the trial endpoint. Overall, repeat bronchoscopy and valve removal or manipulation was performed in 35% of treated patients. 68 patients were randomly assigned to treatment with endobronchial valves (n=34) or usual medical care (n=34). Analysis of the results after exclusion of patients who were unable to complete the study and in whom the valves were permanently removed revealed even greater changes in a number of outcome measures and responder rates in the remaining patients. Baseline FEV_1 was 29% of predicted, residual volume was 218% of predicted, 6MWD distance was 337 m, and total SGRQ score was 59·2—these baseline values indicate that the participants had severe disease, of a similar level to that of participants in the BeLieVeR-HIFi study. The main adverse events observed in the intervention group were exacerbations of COPD and pneumothoraxes. In total, six pneumothoraxes (18%) occurred—three of which settled within 14 days and three of which required removal of a valve. Valves were replaced in a further five patients due to torsion of the bronchus (n=2), pneumonia distal to the valve (n=1) and severe coughing with no perceptible clinical benefit (n=2) and valves were replaced in four patients after migration or dislocation of a valve. The intention-to-treat analysis showed a 20·9% (95% CI 11·1 to 30·7) improvement in FEV_1 in the intervention group compared with a 3·1% improvement (CI –0·4 to 6·6; p=0·002) in the control group.

The exclusion of patients with collateral ventilation or patients in whom valves could not be placed for technical reasons and the re-evaluation of patients in advance of any outcome measures was a particularly wise intervention by the researchers in the STELVIO trial and represents personalised medicine with interventional bronchoscopy. Re-evaluation ensures that procedures or interventions that have a substantial cost, not only in monetary terms but also with respect to adverse events, are only offered to patients who are very likely to benefit. The STELVIO trial also demonstrated the versatility of valve treatment because the valves can be removed, manipulated, and replaced to ensure patients attain maximum benefit. Valve treatment has the unique potential to be completely reversible if the patients experience deterioration in function or symptoms; whereas surgery and other volume reduction techniques, such as endobronchial coils or thermal ablation, are not so readily reversible. Furthermore, this trial confirms that morbidity associated with endobronchial interventions is lower than that observed with surgery.

The STELVIO study[19] showed both statistically significant and clinically meaningful results. The BeLieVeR-HIFi study[18] appears to have less impressive results. Possible factors accounting for the differences in responses include differences in study design because the sham controlled study ensures a much lower potential for a placebo effect; the 6-month endpoint used in the STELVIO trial versus the 3-month endpoint in the BeLieVeR-HIFI study, because patients might need time to recover between the bronchoscopy procedure and evaluation; and technical issues—the valves were expectorated in four patients in the BeLieVeR-HIFi study but expectorated valves were replaced in the STELVIO trial. Provisions for valve adjustment before outcome measurements were not allowed in the BeLieVeR-HIFi study.

Both trials highlighted the need for further product development due to anatomical variations and led to development of a smaller valve with a shorter landing zone to fit in short sub-segments that could not previously be treated in the clinical trials performed with endobronchial valves. Most importantly, these two single-centre trials showed the efficacy of endobronchial valve therapy, which has now been proven to work in selected emphysema patients with absence of collateral flow. The BeLieVeR-HIFi and STELVIO trials also paved the way for the currently ongoing multicentre randomised controlled trials of this therapy (table).

Endobronchial coils

Endobronchial coils are non-blocking, shape-retaining nitinol devices delivered bronchoscopically into the sub-segmental airways to induce parenchymal compression and enhance lung recoil (figure 3). 10–12 coils (size 100–150 mm) are delivered in the most diseased lobes using fluoroscopy to control positioning. One lobe is treated per procedure, and a contralateral lobe is treated 1–4 months later. This treatment was first performed in a very small feasibility trial[20] which showed that the technique was safe. After this trial, the treatment was further developed and optimised in several small feasibility trials[21–23] in patients with heterogeneous or homogeneous emphysema. The proposed mechanism of action of the endobronchial coils, which act independently of collateral flow, is a combination of the physiological effects of lung volume reduction and restoration of the elastic properties of the lung tissue.[24]

The RESET randomised controlled trial[25] investigated endobronchial coils for the treatment of severe emphysema with hyperinflation in three UK centres, with 3 months' follow-up for the primary endpoint (SGRQ). 47 patients with severe emphysema, with both homogeneous and heterogeneous distributions, were randomly assigned to active coil treatment (n=23) or usual care (n=24). Baseline demographics across all participants confirmed patients had severe disease, with a mean FEV_1 of 27·2% of predicted (SD 8·0), a residual volume of 236% of predicted (SD 50·3), 294 m (SD 75) for 6MWD, and an SGRQ total score of 65·2 points (SD 8·7). Most patients were directly discharged the day after the procedure (91%). In the first month after treatment, more adverse events were reported for the coil-treated patients, with two pneumothoraxes, compared with none in the control patients, and with 10% of the coil-treated patients experiencing a COPD exacerbation or pneumonia compared with 4% in the control group. In the period between 30 and 90 days after treatment, no differences in adverse events were seen between the groups. Furthermore, no unanticipated device-related adverse events were reported. At 3 months post treatment, the coil treated group improved by –8·36 points (95% CI –16·24 to –0·47) on SGRQ compared with the control group, with 57% of the coil-treated patients improving at least 8 points, compared with 13% of the patients in the control group (p=0·01). Of the secondary endpoints in the

	NCT identifier	Sponsor	Device	Patients	Centres	Countries	Key inclusion criteria	Primary endpoint	Status	Estimated primary completion date
Impact	NCT02025205	Pulmonx	Zephyr valve *vs* SC	93	8	Austria, Germany, Netherlands	FEV_1 15–45% of predicted; RV ≥200%; absence of collateral ventilation; homogeneous emphysema	% change in FEV_1 at 3 months	Recruitment completed	December, 2016
Liberate	NCT01796392	Pulmonx	Zephyr valve *vs* SC	183	23	USA, Brazil, Netherlands, UK	FEV_1 15–45% of predicted; RV ≥180%; absence of collateral ventilation	% change in FEV_1 at 1 year	Recruiting	June, 2017
Transform	NCT02022683	Pulmonx	Zephyr valve *vs* SC	78	17	Belgium, France, Netherlands, UK, Germany, Sweden	FEV_1 15–45% of predicted; RV ≥180%; absence of collateral ventilation; heterogeneous emphysema	% change in FEV_1 at 3 months	Recruitment completed	May, 2016
Emprove	NCT01812447	Spiration	Intrabronchial valve *vs* SC	270	37	USA, Canada	FEV_1 ≤45% of predicted; RV ≥150%; heterogeneous emphysema	% change in FEV_1 at 6 months	Recruiting	September, 2016
SVS	NCT01812447	Spiration	Intrabronchial valve *vs* SC	100	1	China	FEV_1 ≤45% of predicted; RV ≥150%; heterogeneous emphysema	% change in FEV_1 at 3 months	Recruiting	September, 2016
CELEB	ISRCTN19684749	National Institute for Health Research	Valve *vs* LVRS	76	1	UK	FEV_1 20–60% of predicted; RV >170%; absence of collateral ventilation; heterogeneous emphysema	Change in iBODE at 1 year	Recruiting	March, 2019

NCT=national clinical trial. SC=standard care. FEV_1=forced expiration volume. RV=residual volume. LVRS=lung volume reduction surgery. iBODE=composite of body-mass index, FEV_1, Medical Research Council dyspnoea score and shuttle walk test distance.

***Table*: Ongoing randomised clinical trials assessing endobronchial lung volume reduction**

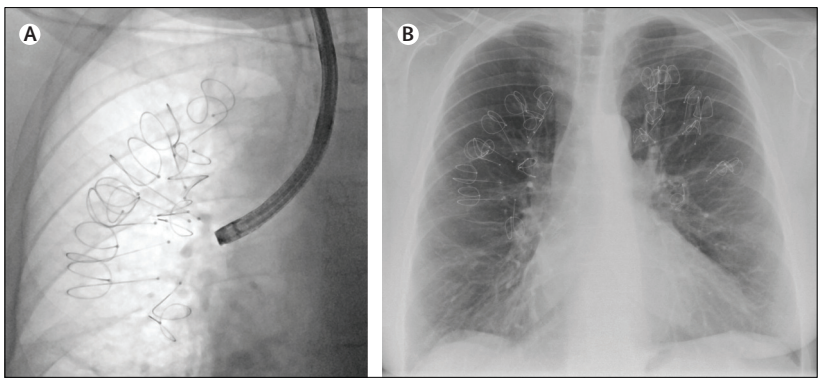

***Figure 3*: Endobronchial coils**
(A) Fluoroscopic image of coils placed with bronchoscopy. (B) Chest radiograph after bilateral upper-lobe treatment with coils.

trial, FEV_1 improved by 10·6% (1·2 to 20·1), residual volume improved by –0·31 L (–0·59 to –0·4), and 6MWD improved by 63·6 m (32·6 to 94·5), for the treatment group compared with control patients. This trial could be criticised for the relatively small number of patients treated (n=23), and the short follow-up period of only 3 months. However, this trial is one of the first to use endobronchial coils in patients with severe emphysema and shows their potential. Furthermore, in the RESET trial, patients with a homogeneous emphysema distribution were successfully treated for the first time. This is crucial, since the efficacy of surgical alternatives for the homogeneous emphysema phenotype is debatable, although some surgical groups continue to operate on selected patients with homogeneous emphysema with good long-term results.[26]

The REVOLENS study[27] was a 1:1 randomised study of endobronchial coil therapy versus usual care in ten centres in France involving 100 patients with bilateral emphysema and severe hyperinflation (respiratory volume >220%). The primary endpoint was the difference between coil treatment and medical therapy in the proportion of patients improving by at least 54 m on the 6MWD at 6 months after treatment. Both groups were followed for 1 year. The baseline characteristics for the treatment group showed a mean FEV_1 of 25·7% of predicted (SD 7·5), residual volume of 271% of predicted (SD 38), 6MWD of 300 m (SD 112), and SGRQ total score of 60·8 points (SD 12·8). Bilateral endobronchial coils were bronchoscopically placed in 47 of the 50 patients in the intervention group. At 1 year, four deaths were recorded in the intervention group, compared with three in the control group. Four pneumothoraxes occurred in the intervention group compared with one in the control group. The rate of COPD exacerbations did not differ between the two groups, but more pneumonias were observed in the endobronchial coil patients (11 *vs* two). The trial met its primary endpoint—18 patients (36%) in the intervention group achieved at least a 54 m increase in the 6MWD compared with nine patients (18%) in the control group (p=0·03). The between-group difference for coil treatment versus usual medical therapy group in the 6MWD at 6 months was 21 m (95% CI –4 to ∞), and was maintained at 21 m at 12 months (–5 to ∞); this difference in 6MWD was mainly driven by a mean reduction of –23 m (–42 to –4) in patients in the usual medical therapy group. At 1 year, FEV_1 was 11% (5·2 to ∞) higher in the treatment group compared to control, mean residual volume differed by –0·36 L (–0·10 to ∞), and mean SGRQ score was –10·6 (–5·8 to ∞). Only 116 patients were screened for participation in the trial to recruit the 100 patients who were included. This high participation suggests that the trial designers attempted to resemble daily practice with few exclusion criteria. Also noteworthy is the approximately 90% follow-up rate at 1 year of all initially randomly assigned patients. One of the major scientific issues with this trial was that the inclusion of emphysema on CT scan was judged by the treating physicians, and no CT core laboratory was used to determine emphysema phenotypes and amount of tissue destruction. Hence, the patients selected or excluded on the basis of their CT scans were not standardised and this excluded group of patients have not contributed to our understanding of which are the ideal patients for this treatment option. The difference in 6MWD between the groups at 6 months after randomisation was small, and greater and more consistent improvements were seen in FEV_1 and SGRQ. At 12 months, the 6MWD was –2 m (–29 to 25) in the treatment coil group and –23 m (–42 to –4) in the usual medical therapy group compared with baseline. A methodological issue might be that at baseline about 60% of the patients were on home oxygen therapy at the time that the 6MWD measurement was taken at the hospital without supplemental oxygen (ie, it might have been better to perform these tests with supplemental oxygen to reflect the patients' daily lives).

The RENEW 1:1 randomised clinical trial investigated the effect of endobronchial coils versus usual care in 315 patients.[28] The primary endpoint was the between-group difference in 6MWD change at 1 year. The baseline characteristics were comparable with the previous coil trials with a mean FEV_1 of 25·7% of predicted (SD 6·3), residual volume of 245·9% of predicted (SD 39·1), 6MWD of 312 m (SD 79·1), and SGRQ total score of 60·1 points (SD 12·8), with 77% of the patients being classified as having homogeneous emphysema on an HRCT scan. At 1 year, a between-group difference of 14·6 m (97·5% CI 0·4 to ∞, p=0·02) in favour of the coil group was observed, with 40·0% of coil patients, and 26·9% control patients reaching the 25 m minimal important difference for 6MWD (p=0·01). The between-group difference for FEV_1 showed a median change of 7·0% (3·4% to ∞; p<0·001), and the between-group SGRQ score improved –8·9 points (–∞ to –6·3 points; p<0·001), all in favour of the treatment group. Excess of death was not observed in the coil group, but more adverse events occurred in the intervention group compared with the control group (pneumonia [20% treatment *vs* 4·5% control], and pneumothorax [9·7% *vs* 0·6%]). Prespecified post-hoc analyses showed significant differences for FEV_1, residual volume, 6MWD, and SGRQ at 1 year after treatment with endobronchial

coils all in favour of patients with a high baseline residual volume (235 patients with residual volume >225%, *vs* 80 with residual volume <225%). Furthermore, more than a third of the patients initially classified as having pneumonia were reclassified as non-infectious coil-associated opacities. These coil-induced mechanistic events (eg, air space consolidation that is possibly a result of a strain effect) were associated with greater reductions in residual volume and greater improvements in quality of life, FEV1, and 6MWD.

All three endobronchial coil trials show a statistically and clinically significant benefit of this treatment at 3 months (RESET),[25] 6 months (REVOLENS),[27] and 1 year (RENEW)[28] for pulmonary function and quality of life, with modest improvements for 6MWD, in patients with very severe emphysema. Long-term data from small open-label studies show a gradual decline of the initial benefit over a 1–3 year period, but some patients had clinically meaningful gains even at 3 years.[29,30] Because the effect of endobronchial coils is independent of collateral ventilation and can be applied in homogeneous emphysema, this therapeutic option can be considered in a broad spectrum of patients with severe emphysema. However, it seems key to only treat patients with very severe hyperinflation, with a residual volume more than 225% of predicted.

75% of the sites in both the RENEW and REVOLENS trials had not done the treatment previously. Thus, future trials will have to show how this therapy performs in experienced centres and shed light on its mechanism of action.

Sclerosing therapies

Vapour

Lung volume reduction with steam—known as bronchoscopic thermal vapour ablation (BTVA)—uses thermal energy from heated water vapour to induce a localised inflammatory response, which causes permanent fibrosis and atelectasis, bringing about volume reduction (figure 4). The major complication associated with this procedure is the inflammatory response in the treated area, which occurs within the first 2–4 weeks after treatment, with clinical symptoms ranging from either none to any combination of fatigue, fever, cough, sputum, dyspnoea, and haemoptysis.[31]

The STEP-UP trial[32] was a 2:1 randomised multicentre trial that enrolled patients with upper lobe-predominant heterogeneous emphysema and gave them staged therapy with vapour. The tissue-to-air ratio was calculated at a segmental level on HRCT to identify the most damaged lung segments and to calculate the dose of vapour energy to be delivered at the treatment site. Patients with very destroyed lower lobes were excluded (tissue-to-air ratio <11% on density measurements). Only one segment was treated at the first treatment session and up to two segments were treated during the second treatment session about 3 months later. The primary endpoints included change in FEV_1 and SGRQ scores between the treatment and control arms. One of the limitations of the STEP-UP trial was the failure to use a blinded sham control design, especially because a subjective endpoint (SGRQ score) was included as a primary endpoint and unlike other treatment approaches, no radiologically visible implants are placed (which could reveal treatment allocation). A less important limitation is the change of the primary endpoint to a 6-month endpoint instead of the originally planned 12-month endpoint. 134 patients were screened and 46 were randomly assigned to vapour therapy and 24 to standard care. The mean FEV_1 for the cohort was 33·5% of predicted and residual volume was 240% of predicted. 40 patients were treated twice in a staged method with the second treatment delivered after 13 weeks. Five patients received only the first treatment and one patient did not receive treatment. At 6 months FEV_1 was 14·7% higher (95% CI 7·8 to 21·5), residual volume was 0·30 L lower (–0·54 to –0·06), and the mean change in SGRQ score was –9·7 (–15·7 to –3·7) in the treatment group compared with the control group. Clinically meaningful improvements were seen in 50% of the intervention group patients versus 13% in controls for FEV_1, 70% versus 39% for SGRQ, and 42% versus 23% for 6MWD. A greater incidence of respiratory exacerbations (24% *vs* 4%) and episodes of pneumonitis (18% *vs* 8%) were seen in the intervention group compared with the control group. One death occurred as a result of acute respiratory failure in the treatment group about 3 months after a COPD exacerbation.

Vapour therapy offers a treatment option in patients with heterogeneous disease, irrespective of the presence of collateral ventilation, with the advantage of targeting only the very diseased segments of the lung while preserving adjacent healthier segments. The treatment can also be performed in stages over time to increase both magnitude and duration of benefit. However, future

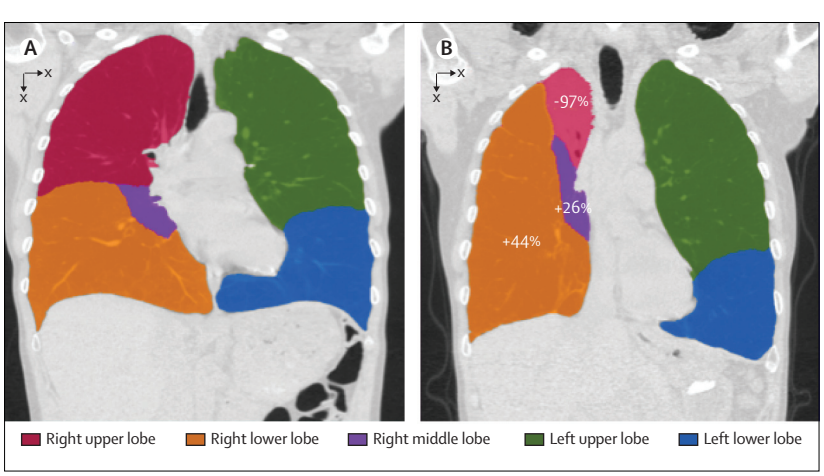

***Figure 4*: Bronchoscopic thermal vapour ablation**
Coronal CT scan showing volume change (A) before and (B) after treatment of right upper lobe with vapour.

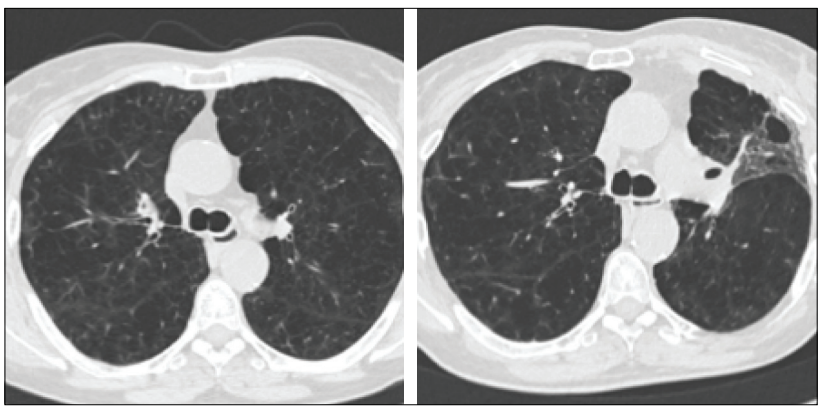

Figure 5: **AeriSeal emphysematous lung sealant therapy**
Axial CT scan before (left) and after (right) treatment with sealant to the lingual segment, with development of ground glass change and fibrosis.

research will have to show a balance between safety and efficacy to make it viable and, to date, it is uncertain how far this therapy will develop.

Sclerosants

AeriSeal emphysematous lung sealant (ELS; Pulmonx, Neuchatel, Switzerland) is another endoscopic lung volume reduction therapy. The AeriSeal system is designed to function at the level of the small airways and alveoli by blocking collateral channels and preventing gas from entering the region, causing absorption atelectasis (figure 5). Thus, its efficacy is not affected by collateral ventilation.

The cross-linking agent used in the AeriSeal system is 4·5 mL of 2·1% (weight/volume) aminated polyvinyl alcohol and 0·5 mL of 1·25% (weight/volume) glutaraldehyde. This solution is mixed with 15 mL of air to produce the AeriSeal foam, which is delivered using a bronchoscope through a catheter into a pulmonary segment.

Once the apposing lung parenchyma surfaces within the treated area are close enough to one another, the adhesive film seals the area closed to ensure a persistent clinical response.[33] The most diseased areas of the lung on HRCT are treated.

In one of the first studies of AeriSeal, conducted in 25 patients, the therapy showed promise for treatment of patients with advanced upper lobe-predominant heterogeneous emphysema.[33] However, this study revealed that AeriSeal was routinely associated with an inflammatory reaction beginning 8–24 h after treatment. The most common side-effects were dyspnoea, fever, infiltrations on chest radiograph, and chest pain. Prophylactic treatment with antibiotics and corticosteroids was introduced in subsequent trials.

The AeriSeal system for hyperinflation reduction in emphysema (ASPIRE) study[34] is thus far the only multicentre, randomised controlled trial to compare AeriSeal treatment with optimal medical therapy in patients with advanced, upper lobe-predominant emphysema. The study was terminated prematurely by the sponsor because of a lack of financial resources after 95 of 300 planned patients were randomly assigned. Data were available at 3 months for 34 patients in the treatment group (n=34) and 23 in the control group (n=23). At 3 months, median FEV_1 improvement was 11·4% (2·0 to 32·0) in the treatment group versus –2·1% (–4·9 to 9·0) in the control group (p=0·0037). The SGRQ total score improved by –11 points (–18 to –1) in the treatment group versus –4 points (–6 to 3) in controls (p=0·026), and the modified Medical Research Council Dyspnoea Score improved by –1·0 points (–2·0 to 0) in the treatment group versus 0 points (–0·8 to 0·8) for control patients (p=0·005).

At 6 months, 18 of 34 (52%) patients in the treatment group still had a response above the minimal clinically important difference for both FEV_1 and 6MWD, with 72% for SGRQ, but these data are based on only 21 patients in the treatment group and 13 patients in the control group. Two deaths occurred in the treatment group and 44% of treated patients experienced an adverse event requiring hospitalisation. AeriSeal treatment is not currently available on the market, and has been returned to preclinical trials in an effort to try and reduce inflammation and create a more predictable response. The available data show the potential of this method, but as with vapour therapy, also emphasise the unacceptable rate of serious adverse events. Before the next clinical trial can be initiated, the inflammatory safety issue must be resolved.

Patient selection

Lung volume reduction should be considered for patients with symptomatic COPD (Global Initiative for Obstructive Lung Disease [GOLD] pulmonary function stages 3 and 4) with evidence of hyperinflation (in our centres, we use residual volume >200% of the predicted value and CT evidence of emphysema), who have stopped smoking, are on optimal medical therapy, and have completed pulmonary rehabilitation, with comorbidities (which can exclude patients from advanced therapies) taken into consideration as well.[35] The CT morphology should guide optimal technique choice. In our opinion, patients with predominant paraseptal emphysema should be considered for surgery. Patients with heterogeneous emphysema and intact lobar fissures should be assessed with the Chartis system to determine collateral ventilation status. Patients with no evidence of collateral ventilation should be considered for lobar occlusion with valves, especially because this therapy is flexible and readily reversible. Patients with collateral ventilation can be considered for treatment with LVRS. The optimal patient group for endobronchial coils is still unclear but the therapy might have a role in patients with marked hyperinflation (residual volume >225%) and a more centrilobular pattern of emphysema. In patients with very heterogeneous disease within a lobe, in which treatment of a whole lobe might be inappropriate, a segmental sclerosing therapy could be considered.[36]

Search strategy and selection criteria

On May 27, 2016, we searched PubMed without language or date restrictions with the search terms of "lung volume reduction", "lung volume reduction surgery", "lung volume reduction coils", "lung volume reduction valve", and "bronchoscopic lung volume reduction". On May 27, 2016, we searched ClinicalTrials.gov without language or date restrictions with the search terms "lung volume reduction" and "interventional studies". References of these trials were searched for additional studies. 1331 publications and trials were identified. Titles, abstracts, and trial registry were screened and 30 possible trials were retrieved as full-text articles.

Conclusion

LVRS was previously widely performed. However, because of the substantial associated morbidity, less invasive endoscopic procedures have been introduced as alternatives for patients who are already on the maximum available treatment. The range of available options enables the treatment of a broader range of emphysema phenotypes. Current evidence shows a valid position for the use of valves in selected patients, with coils being reserved for those with very severe hyperinflation who do not meet valve treatment criteria. Further research is ongoing to develop new treatments such as sclerosants, and to improve positioning of the valve and coil treatments in large randomised controlled trials to further define optimal patient selection (table). Further improvements to both valve and coil implantation techniques are needed, and further insights into pneumothoraxes for valves are required, and a clear mechanism of action and responder profile for coils should be identified. Developments in endoscopic techniques might also revive the use of LVRS, an area of expertise that unfortunately is limited to a few experts worldwide. The results of several ongoing randomised clinical trials will be available soon (table), and will provide additional data regarding the efficacy and safety of lung volume reduction in emphysema. The challenge is to ensure that all lung volume reduction therapies are patient-focused and not limited to local expertise. Hence, the development of expert centres with multidisciplinary teams where all treatment modalities are available is key for both patient care and further development of lung volume reduction therapies.

Contributors

All authors contributed to the manuscript and approved the final version. PLS designed the framework, wrote the outline, procured images, and managed the revisions. FJH worked on the section on sclerosants and revised the report. WHvG did the data analysis, literature search, and implemented the literature cited. GD did the search on ongoing trials, worked on the surgical section, and revised the report. D-JS worked on the section on endobronchial coil therapy, revised the report, and procured images.

Declaration of interests

This work was not formally funded. PLS, D-JS, and FJH have been investigators in trials of endobronchial valves, coils, thermal ablation, AeriSeal, and the airway bypass procedure. GD has been an investigator in a trial of endobronchial valves and coils. WHvG is supported by the European Respiratory Society, Fellowship STRTF 2016, and reports a grant from Novartis to the institution for an investigator-initiated trial outside of the submitted work. The authors' institutions have been reimbursed for trial expenses by the respective device manufacturers. PLS and FJH have consulted for Broncus, CSA Medical, Medtronic, Holaira, Olympus, PneumRx/BTG, and Pulmonx. D-JS has consulted for CSA Medical, Holaira, PneumRx/BTG, and Pulmonx. GD has consulted for PneumRx/BTG.

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