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Lung volume reduction for emphysema using one-way endobronchial valves

An Australian cohort

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Abstract

Emphysema can be associated with gas trapping and hyperinflation, which negatively impacts on quality of life, life expectancy, and functional capacity. Lung volume reduction (LVR) surgery can reduce gas trapping and improve mortality in select patients but carries a high risk of major complications. Bronchoscopic techniques for LVR using one-way endobronchial valves (EBV) have become an established efficacious alternative to surgery. A bi-center retrospective cohort study was conducted on patients with severe emphysema who underwent endoscopic lung volume reduction (ELVR) using Pulmonx Zephyr EBVs. Symptomatic patients with gas-trapping and hyperinflation on lung function testing were selected. Target-lobe selection was based on quantitative imaging analysis and ventilation-perfusion scintigraphy. Successful procedures were determined from clinical review, imaging and follow-up testing. Thirty-nine patients underwent ELVR. Mean pre-procedure forced expiratory volume in 1 second (FEV_1) was 0.75 L, residual volume (RV) was 225% predicted and total lung capacity was 129% predicted. Most common treated-lobe was left upper lobe. Post-procedure pneumothorax occurred in 36.5% of patients with 73% requiring intercostal catheter insertion for drainage. Mean FEV_1 improvement was +140 mL and 57% of patients achieved minimal clinical important difference FEV_1 increase of ≥12%. Maximal mean RV change was −1010 mL with 69% of patients achieving minimal clinical important difference RV decrease of ≥350 mL. Clinician-determined success of ELVR was 78%. Procedure-related mortality was absent. LVR using EBVs is safe and can lead to significant improvements in lung function, particularly reduction of gas trapping and hyperinflation. Occurrence of pneumothorax post-procedure is a complication that must be monitored for and managed appropriately.

Abbreviations: COPD = chronic obstructive pulmonary disease, CV = collateral ventilation, DLCO = diffusion capacity for carbon monoxide, EBV = endobronchial valve, EDS = emphysema destruction score, ELVR = endoscopic lung volume reduction, FEV_1 = forced expiratory volume in 1 second, FI = fissural integrity, LLL = left lower lobe, LVR = lung volume reduction, MCID = minimal clinical important difference, QCT = quantitative computed tomography, RCT = randomized controlled trials, RML = right middle lobe, RUL = right upper lobe, RV = residual volume, TLC = total lung capacity, VQ = ventilation/perfusion.

Keywords: bronchoscopy, chronic obstructive pulmonary disease, emphysema, interventional pulmonology, lung volume reduction

1. Introduction

Emphysema involves destruction of lung parenchyma through the breakdown of alveolar walls resulting in permanent enlargement of air spaces distal to the terminal bronchioles. This leads to impairment of gas exchange and changes in airflow dynamics causing severe gas trapping and hyperinflation. The main cause of emphysema is noxious gas exposure from tobacco smoking. Other associated causes of emphysema include exposure to other inhaled substances such as inorganic dusts, and genetic abnormalities such as alpha anti-1-antrypsin deficiency. Chronic obstructive pulmonary disease (COPD), which includes emphysema, was the 5th most common cause of mortality in Australia in 2018 and 3rd most highest worldwide.[1,2] COPD prevalence was found to be 5% in Australians aged over 45 years and is a leading cause of hospitalizations.[1] Not all patients with COPD have gas trapping and/or hyperinflation, however when present, is a strong predictor of early mortality and is associated with worse quality of life and symptom scores.[3,4]

Treatment for patients with COPD/emphysema includes smoking cessation, inhaled or oral medications (bronchodilators, corticosteroids), supplemental oxygen, pulmonary rehabilitation, surgical lung volume reduction (LVR), and if

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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appropriate lung transplantation. In the National Emphysema Treatment Trial, surgical LVR significantly reduced mortality and improved quality of life and dyspnea scores in a select sub-group of COPD patients.[5] Patients with upper lobe predominant emphysema, severe gas trapping and reduced functional status had best outcomes. However, the LVR patients had significant higher major post-operative morbidity and short-term mortality compared to medical therapy.[5]

Given the limitations of the surgical LVR, less invasive alternatives have been developed. One-way endobronchial valve (EBV) use for LVR was first reported in 2003 and then further studied in the VENT trial.[6,7] Multiple randomized controlled trials (RCTs) since have clearly established the role of EBV in severely obstructed emphysema with associated gas trapping, hyperinflation, reduced exercise capacity, and intact interlobar fissures.[8–11] Endoscopic lung volume reduction (ELVR) is now an established guideline-based therapy for patients with severe COPD.[12] In this retrospective study, we report on a cohort of emphysema patients treated with the Zephyr EBV (Pulmonx Corp., Redwood City, CA) for LVR based on established criteria and consensus guidelines.

2. Methods

This was a retrospective consecutive cohort study of patients who had undergone EBV insertion at 2 centers in Australia between 2015 and 2019. Ethics approval was obtained from the Eastern Health (Victoria, Australia) Ethics Committee (LR07-2018).

Patients had a diagnosis of emphysema with evidence of hyperinflation total lung capacity (TLC ≥ 100%), gas trapping residual volume (RV ≥ 175%) and radiology suitable for EBV insertion. A single respiratory physician performed the clinical assessments and procedures.

All patients had high-resolution computed tomography chest imaging performed to a "valve protocol" (inspiratory axial images with <1.5 mm slice thickness) and subsequent quantitative computed tomography (QCT) analysis via the StratX Lung Analysis Platform (Pulmonx Corporation, Redwood City, CA) to determine fissural integrity (FI) and lobar emphysema destruction scores (EDS). Quantitative ventilation/perfusion nuclear scintigraphy was performed to assess regional perfusion. The "target-lobe" for ELVR was determined algorithmically using the FI, quantification of emphysematous destruction (EDS; percentage of voxels at –910 Hounsfield Units), and lowest scintigraphic perfusion percentage. Baseline measurements collected were age, gender, smoking history, comorbidities, forced expiratory volume in 1 second (FEV_1, FVC, RV, TLC, diffusion capacity for carbon monoxide [DLCO]), QCT and ventilation/perfusion measurements.

Bronchoscopies were performed under general anesthesia or moderate sedation with laryngeal mask intubation. All patients had a bronchoscopic flow assessment (Chartis System, Pulmonx Corp. Redwood City, CA) to confirm the absence of collateral ventilation (CV) in the target-lobe(s) prior to EBV deployment. All patients were admitted to hospital post-procedure for monitoring (minimum of 3 nights). Chest radiography was performed immediately and Day 1 post-procedure. All patients were reevaluated within 4 weeks post-procedure after repeat lung function testing, and then at intervals deemed clinically appropriate.

Procedural data collected were number and type of valves inserted. Post-EBV insertion outcomes assessed were maximal change in lung function (FEV_1, FVC, TLC, RV), radiological evidence of lobar atelectasis, procedural-related adverse events and clinician assessment of response to EBV treatment. Follow-up lung function testing, EBV-associated and non-associated adverse events and repeat procedural data were collected, where available.

Improvement in FEV_1, RV reduction and TLC reduction were used to define long-term physiological success. Radiological evidence of lobar collapse 1-day post-procedure was used to determine initial valve-procedure success.

2.1. Statistical analysis

Data was analyzed using SAS software (version 9.4). Descriptive statistics are provided as mean and standard deviations. Data comparisons were performed using a Student *t* test with significance threshold of $P < .05$. Stepwise logistic regression was performed to determine factors associated with FEV_1 improvement, RV improvement and pneumothorax incidence. FEV_1 and RV response was tested with scintigraphic perfusion and ventilation scores, FI and EDS variables. Pneumothorax incidence was tested with target-lobe scintigraphic ventilation scores, FI, EDS and ipsilateral non-target-lobe EDS variables. Chi-square significance level of 0.3 permitted entry into the regression model and level of 0.35 was required to remain in the model.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

3. Results

3.1. Baseline clinical features

The cohort were 64.1% (25/39) male and mean age was 72 years. Comorbidities were present in 94.9% (37/39) of the cohort and 36% were cardiac. All patients had ceased smoking prior to consideration of EBV treatment, with a mean of 58.5-pack-years history. Mean FEV_1 was 0.75 L (29.4% predicted), mean RV was 5.24 L (227% predicted), mean TLC was 7.76 L (131% predicted) and mean DLCO was 35% predicted (Table 1). Other baseline characteristics are in Table 2.

3.2. Baseline radiologic features

QCT analysis was available for 84.6% (33/39). Mean FI of the target lobes assessed by QCT imaging was 97.38% (±4.40). Mean EDS for target lobes of the full cohort was 63.97% (±9.7), and for specific lobes were: right upper lobe (RUL) 62.4% (±12.3%), RUL + right middle lobe (RML) was 72.0% (±8.5), left upper lobe was 63.8% (±9.1), and the right lower lobe and left lower lobe (LLL) were 67.2% (±6.9) and 58.5% (±10.8) respectively. Mean scintigraphic perfusion distribution to target lobe was 9.97%. Individual scintigraphic lobe distributions are as in Table 3.

3.3. Procedure details

Forty-one EBV-insertion procedures were performed on the 39 patients between February 2015 and August 2019.

Table 1

Lung function measures–mean ± SD from pre- to post-EBV.

	Pre-EBV	Post-EBV	Change (pre to post)
FEV_1 (L)	0.75 ± 0.21	0.90 ± 0.31	0.14 ± 0.30
FEV_1 (% Pred)	29.41 ± 6.83	34.85 ± 8.85	5.18 ± 9.09
RV (L)	5.24 ± 1.16	4.11 ± 1.25	–1.02 ± 1.30
RV (% Pred)	227.41 ± 35.90	176.18 ± 46.65	–45.97 ± 54.51
TLC (L)	7.76 ± 1.66	6.97 ± 1.59	–0.62 ± 1.10
TLC (% Pred.)	130.94 ± 15.44	120.43 ± 18.06	–9.12 ± 18.10

EBV = endobronchial valve, FEV1 = forced expiratory volume in 1 s, RV = residual volume, TLC = total lung capacity.

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Chartis flow assessment data was available for the 41 procedures and negative CV was confirmed in 38 procedures, with the remaining 3 demonstrating "low flow" readings deemed uninterpretable. Most common lobe treated was the left upper lobe (39.0%), followed by LLL, 19.5%; RUL, 19.5%; right lower lobe, 12.2%; and RUL + RML combination, 9.8%. Mean number of valves deployed-per-procedure was 4.3 (range 2–8).

3.4. Procedural outcomes

Target-lobe radiographic atelectasis 1-day post procedure was present in 92.6% (38/41), including the 3 patients with low-flow readings on flow assessment. Mean hospital length of stay data was 8.1 days (range 3–31). Three patients underwent repeat EBV insertion procedures into different target-lobes after initial treatment failure and lack of clinical response.

3.5. Follow-up

Clinician-assessed improvement of symptoms and/or function post-procedure was present in 78% (32/41). Three patients had their EBVs removed due to lack of clinical response and were excluded from final review. One patient proceeded onto lung transplantation, and another is currently awaiting lung transplantation. Five patients died prior to repeat lung function testing and follow-up. All deaths occurred at >3 months post-EBV procedure, and none were deemed related to the procedure. Causes of deaths included sudden cardiac death (n = 1), motor vehicle accident (n = 1) and ischemic colitis (n = 2). The remaining patient died from hypercapnic respiratory failure despite and distant from EBV-insertion procedure.

Table 2

Baseline characteristics.

Variable	N	Mean ± SD	Range
Age (yr)	41	72.4 ± 6.2	57.00–87.00
Smoking history (Pack yr)	41	58.5 ± 28.7	20.00–160.00
FEV_1 (L)	41	0.75 ± 0.21	0.49–1.40
FEV_1 (Percent predicted)	41	29.4 ± 6.8	20.00–50.00
RV (L)	41	5.24 ± 1.16	3.38–7.88
RV (Percent predicted)	41	227.4 ± 35.9	171.00–313.00
TLC (L)	33	7.76 ± 1.66	5.13–11.38
TLC (Percent predicted)	33	130.94 ± 15.44	104.00–170.00
DLCO (L)	33	8.82 ± 3.00	4.50–16.70
DLCO (Percent predicted)	33	34.7 ± 9.4	15.00–55.00
Target lobe fissure completeness (%)	33	97.38 ± 4.40	86.20–100.00
Target lobe emphysema destruction score (–910HU; %)	33	63.97 ± 9.72	38.00–80.00

DLCO = diffusion capacity for carbon monoxide, FEV1 = forced expiratory volume in 1 s, TLC = total lung capacity.

3.6. Adverse events

Most frequent complication post EBV-insertion was pneumothorax in 36.5% (15/41) with 73.3% (11/15) of these requiring intercostal catheter insertion. Seven percent (3/41) required removal of all valves for persisting air-leak. Repeat bronchoscopies were required in 56.1% (23/41) due to loss of effect or complications. Other EBV-related complications diagnosed on bronchoscopy included valve sputum plugging (n = 11), valve displacement/migration (n = 6) and granulation tissue formation (n = 2). Valve replacements were performed in 33.3% (13/39) of patients, and 7.7% (3/39) had valves removed and not replaced. Stepwise logistic regression found that higher ipsilateral non-treated-lobe EDS (P = .01) and treated-lobe destruction scores (P = .21) were associated with pneumothorax occurrence, but not FI.

3.7. Lung function testing

Although lung function for all patients met guidelines, only 33 were able to be sourced for both pre- and post-procedure analyses. Best lung function measures were achieved at mean 253 days (±307.9) post-procedure. Mean post-procedure FEV_1 was 0.9L (±0.3), a mean FEV_1 improvement of 140 mL and 23.1% increase compared to baseline. Fifty-seven percent (19/33) of patients had a ≥12% increase in FEV_1. Mean post-procedure RV was 4.11 L (±1.25), representing mean RV reduction of –1020 mL and 17.9% decrease compared to baseline. Sixty-nine percent (23/33) of patients had an RV reduction ≥350 mL. Mean post-procedure TLC was 6.97 L representing mean TLC decrease of –620 mL and 7.0% compared to baseline. Mean post-procedure DLCO increased by 1.77% compared to baseline. Stepwise logistic regression found FEV1 response was associated with treated-lobe lower scintigraphic perfusion (P = .07) and higher scintigraphic ventilation scores (P = .03), FI (P = .096) and EDS (P = .17). RV response was found to be associated with treated-lobe scintigraphic perfusion (P = .22) and ventilation scores (P = .19), but not FI or EDS.

4. Discussion

To our knowledge, this is the largest Australian cohort reported to undergo ELVR for emphysema with gas trapping, using published consensus expert recommendations.[13] Most of our cohort had a clinically significant response to the ELVR treatment. Safety of EBV treatment was also demonstrated, with no major associated procedural mortality.

Outside of a clinical trial, it can be difficult to separate the magnitude of comorbidities limiting a patient's functional status. Over one-third of our patients had significant comorbidities such as cardiac disease, yet still reported significant improvements in breathlessness, functional status, and lung function improvement post-ELVR. This highlights that appropriate patient selection for ELVR (based on guidelines), particularly in those with gas trapping and hyperinflation, can lead

Table 3

Lobar quantitative computed tomography (QCT) analysis and ventilation-perfusion scintigraphy results.

	Lobe treated				
Variable	LLL (n = 8)	LUL (n = 16)	RLL (n = 5)	RUL (n = 8)	RUL ± RML (n = 4)
Fissure completeness (%)	97.8 ± 5.4	97.5 ± 4.2	98.8 ± 2.6	95.0 ± 6.1	98.6 ± 1.3
Emphysema destruction score (% at –910HU)	58.5 ± 10.8	63.8 ± 9.1	62.4 ± 12.3	67.2 ± 6.9	72.0 ± 8.5
Ventilation (%)	7.5 ± 6.0	8.2 ± 4.5	11.3 ± 5.4	7.4 ± 3.8	16.2 ± 11.6
Perfusion (%)	8.7 ± 9.12	8.1 ± 3.7	11.3 ± 4.1	7.0 ± 3.8	23.7 ± 4.9

Values reported as mean ± SD.

LLL = left lower lobe, LUL = left upper lobe, RLL = right lower lobe, RML = right middle lobe, RUL = right upper lobe.

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to a high treatment response.[12] Seventy-eight percent of the cohort achieved meaningful improvements in symptoms, function status, and lung function. The remaining 22% failed to achieve benefit due to a combination of factors including lack of expected lobar volume reduction of the treated-lobe, and complications necessitating valve removal. The lack of success does highlight ELVR as a reversible procedure and removal is relatively easy, if necessary.

Multiple RCT assessing EBVs have utilized a minimal clinical important difference (MCID) of FEV_1 improvement of ≥12% or RV reduction of ≥350 mL as a measure of success.[7,9,11,14] In our cohort, 56% of patients were able to achieve the same MCID FEV_1 improvement and 76% achieved the same MCID for RV reduction. A major difference in our study was using best lung function testing results achieved post-treatment, compared to the EBV RCTs which had set follow-up testing intervals between 3 months and 12 months. The average interval at which best lung function was reached was ~8.5 months post-procedure, which is novel information from a real-world treatment perspective.

The level of improvements seen in this cohort are similar to those in previously published bronchoscopic LVR trials.[7,9,11,14] In the multicentre TRANSFORM RCT, EBV-treated patients achieved a mean FEV_1 improvement of 140 mL (20.7% change) after 6 months when compared to baseline.[9] Our cohort achieved a similar value of 140 mL, which equated to a greater percentage change of 23.3% when compared to baseline. In the TRANSFORM cohort, RV was reduced by an average of 660 mL at 6 months, whereas in our patients that value was greater at 1010 mL.[9] Whilst these improvements are difficult to directly compare due to different methodologies, they are nonetheless substantial.

The availability of QCT imaging to categorize interlobar FI and simultaneously quantify the distribution of lobar emphysema has become a vital tool in determining suitability for EBV insertion. The average FI in this cohort was above 95%. This level of FI has previously been reported to be sufficient for exclusion of CV without the need for physiologic confirmation with Chartis; however, all patients in this cohort underwent confirmation of CV negative status with Chartis prior to valve insertion.[10] EDSs for all treated-lobes were above the recommended 50% cutoff, with the highest value being in the RUL + RML and the lowest in the LLL. The appropriate selection of target-lobes for treatment based on both the FI and emphysema score directly correlates with detected lung function improvements.

EBV use is associated with complications including pneumothorax, valve migration, valve malfunction, and granulation tissue formation.[12] Pneumothorax is the most severe reported complication with previously reported incidence rates of 4% to 27%.[12] The management of the pneumothorax and the potential for development of persistent air-leaks or bronchopleural fistulas can significantly impact LOS and potentially lead to deconditioning in the affected patients, if slow to heal.[15] Expert Panel guidance on the management of post-LVR pneumothorax has been published and was followed in this cohort.[15] Our cohort had a slightly higher incidence of pneumothorax post-EBV insertion at 36.5% compared to the major EBV trial cohorts. Further analysis found this to be associated with the FI, and not surprisingly, ipsilateral non-treated lobe EDS. Most pneumothoraces in this cohort required intercostal catheter-drainage and 3 patients required temporary valve removals, but there was no other major associated mortality or morbidity. LOS was an average of 8.1 days, with a minimum stay of 3 nights established by protocol. As with other major bronchoscopic interventions, repeat procedures have become a recognized and accepted part of follow-up with just over half in this cohort requiring repeat bronchoscopies to review valve placement and function, clear tenacious secretions, or perform valve revisions.[16] Another novel observation in our cohort was the high incidence of sputum plugging on repeat bronchoscopy. All patients were selected out for bronchitis and bronchiectasis, as per the EBV selection guidelines, and had no sputum production at time of EBV insertion. We theorize that the sputum plugging might be attributed to airway irritation from deployed EBVs.

Limitations of this study include its retrospective nature and associated selection bias, as well as the lack of a comparator group. Data comparisons and quality are sub-optimal due to variance in time intervals of repeat testing and missing data that could not be located, meaning that several confounders limit interpretation of results. There was also no formal assessment of functional capacity, such as with 6-minute walk testing, and symptoms, such as the Medical Research Council dyspnea scale measurements after EBV procedures, which limits the clinical assessment of improvements. However, our data highlights the real-world nature of the treated cohort where respiratory dyspnea questionnaires are not routinely used in routine clinical practice. An advantage of the study is that a single physician performed all valve placement procedures and so procedural aspects and assessments are consistent. Other advantages include generalisability due to the "real-world" population selected and the cohort size, which is the largest reported in Australia.

In conclusion, this study demonstrates that ELVR using endobronchial valves in patients selected based on clinical trial-determined criteria, leads to significant radiological atelectasis, gas trapping and hyperinflation reduction and spirometry improvement, with simultaneous benefits in self-reported functional status, and breathlessness in a real-world setting. This is with its disadvantages of pneumothoraces and repeat endoscopies, but no associated mortality.

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