Chronic Obstructive Pulmonary Diseases:
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Journal Club

Ron Balkissoon, MD, MSc, DIH, FRCPC[1]

Abbreviations: lung volume reduction surgery, **LVRS**; forced expiratory volume in 1 second, **FEV_1**; National Emphysema Treatment Trial, **NETT**; video-assisted thoracosopic surgical approach, **VATS**; computed tomography, **CT**; forced vital capacity, **FVC**; endobronchial valve, **EBV**; confidence interval, **CI**; high resolution CT, **HRCT**; modified Medical Research Council dyspnea scale, **mMRC**; residual volume, **RV**; total lung capacity, **TLC**; % predicted, **% pred**

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1 Denver, Colorado

Address correspondence to:

Ron Balkissoon, MD, MSc, DIH, FRCPC
balkissoonr@NJHealth.org

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Introduction

A meta-analysis of several clinical studies demonstrated that lung volume reduction surgery (LVRS) produces about a 0.32 (L) weighted mean improvement in forced expiratory volume in 1 second (FEV_1) at 6 months and 0.280 (L) improvement at 12 months compared to standard medical therapy.[1] The National Emphysema Treatment Trial (NETT) demonstrated a survival benefit in individuals with predominantly upper lobe emphysema and low exercise capacity after pulmonary rehabilitation.[2] Even with the best selection criteria there remains a 3%-5% perioperative risk of death with LVRS.[2] Further, not all patients are suitable candidates for LVRS even with the less invasive video-assisted thoracoscopic surgical (VATS) approach. Endobronchial one-way valves inserted into segmental and sub-segmental bronchi have been shown to lead to lobar or segmental collapse as a means of achieving lung volume reduction. Early trials showed statistically but not clinically significant improvements in FEV_1 and other outcomes.[3-5] The small effect size from the Endobronchial Valve for Emphysema Palliation Trial (VENT) was considered insufficient to warrant approval by the U.S. Food and Drug Administration approval.[4] Sciurba and colleagues found, however, that in a post hoc analysis patients with markedly heterogeneous disease and intact inter-lobar fissures improved significantly more than those that did not have these traits.[4] The recently published studies presented below examine the outcomes in this highly selected group of patients as well as the accuracy of computed tomography (CT) identification of intact inter-lobar fissures versus an endobronchial catheter system (Chartis, Pulmonx, USA) used to detect the evidence of collateral ventilation.

Abstract 1
Endobronchial valves for emphysema without interlobar collateral ventilation

Klooster K, ten Hacken NH, Hartman JE, Kerstjens HA, van Rikxoort EM, Slebos DJ. *N Engl J Med.* 2015;373(24):2325-2335.

Background:
Bronchoscopic lung-volume reduction with the use of one-way endobronchial valves is a potential treatment for patients with severe emphysema. To date, the benefits have been modest but have been hypothesized to be much larger in patients without inter-lobar collateral ventilation than in those with collateral ventilation.

Methods:
We randomly assigned patients with severe emphysema and a confirmed absence of collateral ventilation to bronchoscopic endobronchial-valve treatment (EBV group) or to continued standard medical care (control

group). Primary outcomes were changes from baseline to 6 months in forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and 6-minute walk distance.

Results:
Eighty-four patients were recruited, of whom 16 were excluded because they had collateral ventilation (13 patients) or because lobar segments were inaccessible to the endobronchial valves (3 patients). The remaining 68 patients (mean [±standard deviation] age, 59±9 years; 46 were women) were randomly assigned to the EBV group (34 patients) or the control group (34). At baseline, the FEV_1 and FVC were 29±7% and 77±18% of the predicted values, respectively, and the 6-minute walk distance was 374±86m. Intention-to-treat analyses showed significantly greater improvements in the EBV group than in the control group from baseline to 6 months: the increase in FEV_1 was greater in the EBV group than in the control group by 140ml (95% confidence interval [CI], 55 to 225), the increase in FVC was greater by 347ml (95% CI, 107 to 588), and the increase in the 6-minute walk distance was greater by 74m (95% CI, 47 to 100) (P<0.01 for all comparisons). By 6 months, 23 serious adverse events had been reported in the EBV group, as compared with 5 in the control group (P<0.001). One patient in the EBV group died. Serious treatment-related adverse events in this group included pneumothorax (18% of patients) and events requiring valve replacement (12%) or removal (15%).

Conclusions:
Endobronchial-valve treatment significantly improved pulmonary function and exercise capacity in patients with severe emphysema characterized by an absence of inter-lobar collateral ventilation. (*Funded by the Netherlands Organization for Health Research and Development and the University Medical Center Groningen; Netherlands Trial Register number, NTR2876.*)

Comments:

This was a government funded non-industry sponsored trial. This was an open label trial where patients and investigators knew assignments. The study had a relatively small sample size that was actually increased from the original sample size which had been based on the VENT trial. The increase was necessary due to the number of pneumothoraces and less than expected improvements in FEV_1 compared to the control group. The groups were fairly well matched except for gender wherein there were 53% females in the EBV group versus 82% in the control group. The control group was crossed over to EBV after 6 months. The patient population had severe to very severe disease, (mean age 58, 37 pack year smoking history, FEV_1 29% predicted [%pred], mean modified Medical Research Council [mMRC] dyspnea scale scores 2.7, residual volume [RV] 218%, total lung capacity [TLC] 130%, RV/TLC 60%, 6 min walk test 370 meters, St. George's Respiratory Questionnaire 59), but they would likely be considered candidates for lung volume reduction surgery. We are not provided with information regarding the nature of standard therapy for the control group. Individuals were screened using high resolution CT (HRCT) for lobar intactness and then assessed for collateral ventilation using the Chartis catheter system. The Chartis system inserts a catheter into segments and allows air out but no air to enter, if air ceases to be released it indicates the absence of collateral ventilation. Thirteen of 84 (15%) individuals were excluded on the basis of the Chartis assessment. Only unilateral EBV placement of 2-7 valves in a single lobe was performed. Eighteen of 34 (53%) individuals in each group were deemed to have homogenous emphysema (defined as less than 15% difference in percent of target lobe voxels below -950 Hounsfield units) by HRCT evaluation. Previous studies suggest such patients have less favorable outcomes. Improvements in FEV_1 were modest, however, all outcomes exceed minimal clinical important differences for these variables. Further, the control individuals that crossed over and had valve insertion had similar improvements at their 6-month mark. Perhaps results may have been more impressive if it was bilateral lung instead of unilateral EBV insertion.

Considering that one of the aims of EBV lung volume reduction is to reduce the morbidity there were a significant number of adverse events (23). Twelve of 34 EBV patients had repeat bronchoscopy to remove valves or replace valves due to pneumothorax, valve migration, torsion of left lower lobe bronchus after left upper lobe treatment, pneumonia distal to valve, valve dislocation due to granulation tissue and/or persistent cough or dyspnea. There were no complications for those who had valves removed. All fully recovered. Pneumothorax occurred in 6 of 34, 1 needed valves temporarily removed

and 2 permanently removed. Pneumothorax occurred within 1 day for all 6 individuals and while they were in still in the hospital. There was 1 death in the treatment group due to end stage COPD not deemed to be valve related. Given the relatively modest improvements and the substantial morbidity in the EBV treated group it remains debatable as to whether the benefits outweigh the risks compared to LVRS.

Abstract 2
Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFi study): a randomized controlled trial

Davey C, Zoumot Z, Jordan S,et al. *Lancet*. 2015;386(9998):1066-1073.

Background:
Lung volume reduction surgery improves survival in selected patients with emphysema, and has generated interest in bronchoscopic approaches that might achieve the same effect with less morbidity and mortality. Previous trials with endobronchial valves have yielded modest group benefits because when collateral ventilation is present it prevents lobar atelectasis.

Methods:
We did a single-center, double-blind sham-controlled trial in patients with both heterogeneous emphysema and a target lobe with intact interlobar fissures on CT of the thorax. We enrolled stable outpatients with chronic obstructive pulmonary disease who had an FEV_1 of less than 50% predicted, significant hyperinflation (total lung capacity >100% and residual volume >150%), a restricted exercise capacity (6 min walking distance <450m), and substantial breathlessness (mMRC dyspnea score ≥3). Participants were randomized (1:1) by computer-generated sequence to receive either valves placed to achieve unilateral lobar occlusion (bronchoscopic lung volume reduction) or a bronchoscopy with sham valve placement (control). Patients and researchers were masked to treatment allocation. The study was powered to detect a 15% improvement in the primary endpoint, the FEV_1 3 months after the procedure. Analysis was on an intention-to-treat basis. The trial is registered at controlled-trials.com, ISRCTN04761234.

Findings:
Fifty patients (62% male, FEV_1 [% predicted] mean 31.7% [standard deviation 10.2]) were enrolled to receive valves (n=25) or sham valve placement (control, n=25) between March 1, 2012, and Sept 30, 2013. In the bronchoscopic lung volume reduction group, FEV_1 increased by a median 8.77% (IQR 2.27-35.85) versus 2.88% (0-8.51) in the control group (Mann-Whitney p=0.0326). There were 2 deaths in the bronchoscopic lung volume reduction group and 1 control patient was unable to attend for follow-up assessment because of a prolonged pneumothorax.

Interpretation:
Unilateral lobar occlusion with endobronchial valves in patients with heterogeneous emphysema and intact interlobar fissures produces significant improvements in lung function. There is a risk of significant complications and further trials are needed that compare valve placement with lung volume reduction surgery.

Comments:

This is a well-designed non-industry sponsored study. It is one of the few valve trials to have a sham valve placement control group and the assessment team was different from the procedure team. It had a relatively small sample size of only 50 individuals but it was powered according to results of the VENT trial. The patient population had severe disease, mean age 62, 54 pack year history, FEV_1 31% pred, RV 232% pred, TLC 137% pred, RV/TLC 62%, mMRC score 4, 6-minute walk distance 338, m Peak VO_2 0.89 (L/min), SGRQ 72.13. Patients were on inhaled corticosteroids, long-acting beta agonists, and long-acting muscarinic antagonists as tolerated. The follow-up was rather short at only three months. The procedures were all done by a single interventional pulmonologist. The procedure was performed on only 1 lung and perhaps there may have been more impressive improvements if both lungs were done but the high risk of pneumothorax makes it prudent to do only 1 lung at a time. Inclusion was based on CT assessment. While a panel of radiologists assessed if fissures were intact (90% oblique fissure visible) and if heterogeneity existed between lobes (at least 1 point difference in CT NETT scoring system), individuals also had a Chartis catheter evaluation for collateral ventilation. Interestingly 4 of 25 assigned to the treatment arm had collateral ventilation by

Chartis evaluation. Retrospective review indicated that the Chartis assessment predicted better outcome with virtually all responders in the EBV group showing absence of collateral ventilation in the Chartis system. The rationale for developing endobronchial valve insertion techniques has been to achieve lung volume reduction without the morbidity and mortality associated with lung volume reduction surgery and/or to have an alternative for patients who are too ill to undergo surgery. Based on a review of this participant cohort physiology, they would likely have been considered healthy enough to undergo LVRS. There were 2 patients who developed pneumothoraces in the EBV group (8%) versus 1 in the Control group (4%) and there were 2 deaths in the EBV group, (1 end stage COPD, the other developed respiratory failure following difficult valve removal). Hence, it is debatable as to whether this trial demonstrated efficacy with less morbidity and mortality compared to LVRS.

Abstract 3
The accuracy of computed tomography to predict completeness of pulmonary fissures. A prospective study

Kent MS, Ridge C, O'Dell D, Lo P, Whyte R, Gangadharan SP. *Ann Am Thorac Soc.* 2015;12(5):696-700.

Rationale:
Endobronchial valves are a potential alternative to lung volume reduction surgery for advanced emphysema. The greatest improvements in pulmonary function are seen in patients with complete pulmonary fissures, as determined by CT. However, the accuracy of CT to predict completeness of pulmonary fissures has not been compared with the reference standard of direct observation during thoracic surgery.

Objectives:
To determine the accuracy of CT scans to predict completeness of pulmonary fissures.

Methods:
We conducted a double-blind, prospective trial in which completeness of pulmonary fissures was evaluated by direct observation during thoracic surgery. Preoperative CT scans were independently reviewed by 2 dedicated thoracic radiologists and completeness of the fissures was recorded and compared with intraoperative findings.

Measurements and Main Results:
The fissures of 46 patients were evaluated. The positive predictive value of CT scan to detect a complete fissure was 100% for the right major fissure and 75% for the left fissure, but only 33% for the right minor fissure. CT scans had a negative predictive value of 29% in evaluation of the right major fissure.

Conclusions:
CT scans overestimate completeness of the right minor fissure and underestimate completeness of the right major fissure. These findings may have implications for the use of CT scans to select patients for endobronchial valve insertion.

Comments:

This study, utilizing intraoperative evaluation of the fissures, provides an excellent reference standard for evaluating the ability of CT scan evaluation to discern the intactness of the fissures. The study participants were patients scheduled for VATS or open thoracotomy. Of the 48 participants only 15 had COPD and over half of them only had Stage I and none of the study participants had Stage IV and only 3 had Stage III. Collateral ventilation develops after birth and apparently is more common in patients with emphysema,[6] hence this may not be a representative population. The finding that CT scans may overestimate the intactness of the minor fissure is of clinical import given that collateral circulation from the middle lobe could indeed reduce the chances of successful upper lobe atelectasis despite successful EBV occlusion of all upper lobe segments.

Abstract 4
Outcomes of endobronchial valve treatment based on the precise criteria of an endobronchial catheter for detection of collateral ventilation under spontaneous breathing

Herzog D, Thomsen C, Poellinger A, et al. *Respiration.* 2016;91(1).

Background:
Endoscopic lung volume reduction with valves is a valid therapeutic option for COPD patients with severe

emphysema. The exclusion of interlobar collateral ventilation is an important predictor of clinical success.

Objectives:
Recently, a catheter-based endobronchial in vivo measurement system (Chartis, Pulmonx, USA) has become routine in the clinical evaluation of collateral status in target lobes, but the criteria for phenotyping collateral ventilation by Chartis evaluation have not yet been defined. We asked the questions, how many phenotypes can be identified using Chartis, what are the exact criteria to distinguish them, and how do the Chartis phenotypes respond to valve insertion?

Methods:
In a retrospective study, 406 Chartis assessments of 166 patients with severe COPD were analyzed. Four Chartis phenotypes, collateral ventilation positive (CV+), collateral ventilation negative (CV-), low flow (LF) and low plateau were identified. Fifty-two patients without collateral ventilation were treated with valves and followed for 3 months.

Results:
The Chartis phenotypes were discriminated with respect to decline in expiratory peak flow, increase in resistance index and change in total exhaled volume after 1, 2, 3, 4 and 5 minutes of measurement time ($p<0.0001$, ANOVA), and the cutoff criteria were defined accordingly. To examine the application of these phenotyping criteria, students applied them to 100 Chartis assessments, and they demonstrated almost perfect inter- and intra-observer agreements (x03BA; >0.9). Compared to baseline, collateral negative and low flow patients with ipsilateral collateral ventilation negative lobe showed an improvement in FEV_1 ($p<0.05$), vital capacity ($p<0.05$) and target lobe volume reduction ($p<0.005$) after valve insertion.

Conclusion:
This study describes the most prevalent Chartis phenotypes.

Comments:

This study is included as it further supports the utility of the Chartis catheter system and suggests phenotyping criteria that may further assist in assessing which patients are best candidates for EBV intervention.

Summary

While the results of the clinical trials above show some promise, there remain questions about the benefits versus risks of EBV lung volume reduction. The high rate of pneumothoraces in the Klooster trial versus the Davey trial likely reflects the more stringent selection for patients without collateral ventilation. Pneumothoraces likely occur in this patient population as a result of rupture of bullae or blebs and/or change in conformation of the lung with complete atelectasis of the target lobe. Hence the use of the Chartis catheter likely enriches the number of patients in the EBV group who achieve significant lobar collapse and thus increases the risk of pneumothorax. Further, it is clear that not all patients are good candidates for EBV, for example if the bronchus is too short it may lead to early expectoration. For patients who require valve removal, more difficult extractions may require rigid bronchoscopy to remove a valve and cardiothoracic surgical back up should be available. Given the high pneumothorax rate it is not necessarily an option to consider for those "too ill" for LVRS. Hence, it remains unclear where EBV insertion should be considered. Should it be used in early stages, as a bridge to LVRS or to lung transplantation? To answer these and other questions clearly there is a need for larger prospective trials directly comparing LVRS to EBV insertion.

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