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Endobronchial valve lung volume reduction and small airways function

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At a Glance Commentary

Scientific knowledge on the subject:

Lung volume reduction (LVR) has been shown to improve lung function, exercise capacity, quality of life, and survival in selected individuals with severe emphysema and hyperinflation. However, the impact of LVR on the function of the small airways, the principal site of airflow obstruction in COPD, is largely unknown. Sensitive physiological techniques of oscillometry and ventilation distribution can provide additional insight into mechanisms of benefit from these procedures.

What this study adds to the field:

LVR with endobronchial valves led to improvements in oscillometry and multiple breath nitrogen washout measures reflecting reductions of airflow limitation and ventilation inhomogeneity. These data provide mechanistic support for the beneficial impact of bronchoscopic LVR on peripheral lung function.

The small airways (those <2mm internal diameter) offer little resistance to airflow in health, however the response to repetitive and continual insult by inhaled noxious particles causes them to become the principal site of impediment to airflow in chronic obstructive pulmonary disease (COPD). As disease progresses, several pathophysiological mechanisms collectively lead to emphysema and lung hyperinflation, recognized as significant contributors to the patient's perception of breathlessness and activity limitation that predicts not only the risk and severity of exacerbations, but also all-cause mortality. These observations have stimulated interest in lung volume reduction (LVR) techniques, lung volume reduction surgery (LVRS) and more recently, placement of endobronchial valves (EBVs) which limit air entry but permit unimpeded expulsion of air and mucus, to deflate the lung in an attempt to restore respiratory mechanics. Accruing evidence supports the concept of LVR to improve lung function, exercise capacity, quality of life, and survival. Volume reduction is the key driver of the benefit(**1**).

Although the small airways are the principal site of disease pathogenesis, the effects of LVR on small airways function are largely unknown. Bilateral LVRS undertaken in 29 patients with severe emphysema has demonstrated more efficient small airways lung ventilation with scintigraphic imaging of regional lung ^{133}Xe gas washout(**2**). Oscillometry in 23 patients whose heterogeneous emphysema or emphysematous bullae had been treated with histoacryl gel, an experimental 'biological' LVR not clinically approved for routine practice, showed a decreased R_{5Hz}, with unaltered X_{5Hz}(**3**).

Here, we study the impact on lung mechanics of EBVs. We hypothesized that EBVs implanted in the proximal bronchi of the most severely diseased lung lobe(s), would lead to functional improvements in the peripheral lung. Small airways function was assessed using oscillometry and ventilation distribution tests.

Methods

In a prospective observational study (ethics reference 14/SC/0193), COPD patients with severe emphysema and without collateral ventilation, underwent EBV placement (Zephyr, PulmonX, USA). During stable disease state before and three months after the procedure, patients underwent clinical phenotyping: symptom scores (mMRC and SGRQ), functional exercise capacity (six-minute walk distance), radiological assessment, lung function testing. Post-bronchodilation (400mcg albuterol), routine body plethysmography was followed by impulse oscillometry (IOS; Cardinal Health, Hoechberg, Germany) and multiple-breath nitrogen washout (MBN_2W) testing (PK-Morgan, Rainham, UK), as described previously(**4**). Wilcoxon signed-rank tests were performed using GraphPad Prism (v8, San Diego,CA), with significance at $p<0.05$.

Results

Twelve COPD patients (five female) participated with a baseline median mMRC score 2.5 and SGRQ-total score 50.9 and features of very severe airflow obstruction (FEV_1 28% predicted), hyperinflation (RV 225% predicted), and radiological signs of emphysema (**Table 1**). Three months post procedure, with a radiologically verified median volume reduction of 730mls, significant gains were observed in spirometry, static lung volumes (RV and RV/TLC), exercise capacity, and SGRQ-activity score (**Table 1**). Distinct improvements were obtained for IOS indices of reactance (X_{5Hz}; p=0.013 and X_{in5Hz}-X_{ex5Hz}; p=0.010)(**5,6**), and for MBN_2W indices of lung clearance index (LCI; p=0.006) and alveolar mixing efficiency (AME; p=0.001)(**7**) (**Table 1**).

During follow-up, four patients developed pulmonary infections: two pneumonias, two COPD exacerbations. No pneumothoraces were recorded.

Discussion

We have shown that LVR utilising EBVs, with resulting CT-measured and plethysmography-derived lung volume reductions that were clinically meaningful, led to significant changes in the oscillometry index of X_{in5Hz}-X_{ex5Hz} (difference between inspiratory and expiratory reactance), a surrogate measure of expiratory flow limitation (EFL) in COPD(**5**). The consistency of our X_{in5Hz}-X_{ex5Hz} data corroborates previous reports of how pulmonary mechanics of the peripheral airways are best assessed in obstructive airways disease(**6**). Reactance normally reflects the elastic and inertial properties of the respiratory system but in the presence of EFL, the oscillatory signal is unable to pass through the choke points, reducing the apparent compliance during expiration, and this is aggravated by worsening hyperinflation. Mechanistically, we propose b-LVR decreases EFL of the small airways as observed by a reduction in reactance at 5Hz. We also observed improvement in MBN_2W indices LCI and AME reflecting a more even ventilation distribution throughout the lung(**7**), consistent with findings from a scintigraphic imaging study showing more efficient gas mixing(**2**). In patients where the acinar component of ventilation (Sacin) is the predominant driver of abnormal ventilation distribution, AME may suffice to monitor the impact of EBVs(**7**). Mechanistically, improved ventilatory inhomogeneity may explain the improved oxygen kinetics observed following LVR(**8**).

Emphysema with hyperinflation is a hallmark of severe COPD, with substantial loss of terminal bronchioles, destruction of the elastic scaffold maintaining patency of airways and facilitating passive recoil, and compromising tissue with functional potential(**9**).

Lung volume reduction aims to disencumber the mechanically disadvantaged ventilatory pump, deflating redundant parenchyma, reviving less diseased tissue, and re-tensioning the remaining airway network(**9**). This is conceptually attractive to explain the improvement of the physiological small airway function indices observed here together with the decrease in RV. Not unexpectedly, there was a significant residual impairment in small airways function persisting after valve implantation, as illustrated by S_{acin} (**Table 1**). Post procedure, S_{acin} was compatible with values previously observed in COPD(**10**), and which could be attributed to the extensive loss of terminal bronchioles in addition to emphysema.

When assessing small airways function with physiological tests in interventional studies, it is important to consider the volumetric effect. That is, purely on volumetric grounds, a reduction in ventilated FRC would normally increase R_{5Hz} and decrease X_{5Hz} (i.e., make X_{5Hz} more negative). If we consider small airways function by focusing on R_{in5Hz} and X_{in5Hz}, irrespective of EFL, neither of these indices changed post-EBVs (**Table 1**). As mentioned above, this could represent a counter-balancing effect of the ventilated FRC decrease and signal a small improvement in small airway mechanics over and above the purely volumetric effect of EBV lung volume reduction. LCI and AME are inherently less sensitive to FRC and represent physiological evidence of improved ventilation distribution akin to that observed by radioisotopes in similar patients(**7**). Importantly, adverse events did not appear to impact on three-month outcomes. Our study was uncontrolled and unblinded and did not allow identification of individual lobar expansion, which would only have been possible if additional CT images per patient had been obtained.

In conclusion, our data provide mechanistic support for the benefits of LVR with proximal placement of EBVs, in improving small airways function in patients with severe emphysema and hyperinflation.

DECLARATION OF INTERESTS

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