

A randomised controlled study of Bronchoscopic Lung Volume Reduction with endobronchial valves for patients with Heterogeneous emphysema and Intact interlobar Fissures: the BeLieVeR-HiFi study

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Scientific summary

The BeLieVeR-HiFi study

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Scientific summary

Background

Despite optimal pharmacological therapy and pulmonary rehabilitation, patients with chronic obstructive pulmonary disease (COPD) remain significantly disabled. Emphysema, the destruction of lung parenchyma, is an important feature of the disease. Loss of lung elastic recoil leads to airflow obstruction, gas trapping and increased operating lung volumes. When the condition is heterogeneous, the worst-affected areas of lung expand disproportionately, restricting the ventilation of relatively more healthy areas. Lung volume reduction surgery (LVRS), resecting the worst areas of lung, has been clearly shown to improve outcomes in selected patient groups. The surgical intervention is, however, associated with significant morbidity and an early mortality rate of about 5%. There is therefore considerable interest in developing novel treatment approaches that can reduce lung volumes and gas trapping, either more safely than LVRS or in patients for whom LVRS is not an option. Studies have to date demonstrated modest overall group benefits with the placement of endobronchial valves in COPD. We hypothesised that it would be possible to identify a group of COPD patients prospectively with heterogeneous emphysema and intact interlobar fissures in whom lobar occlusion, and hence lung volume reduction, could be achieved, both to a significant degree and consistently.

Objectives

We sought to address the following questions:

1. Does endobronchial valve placement in this subgroup of COPD patients lead to a significant improvement in airflow obstruction [forced expiratory volume in 1 second (FEV₁)] compared with control patients?
2. Does endobronchial valve placement in this group lead to significant improvement in lung volumes [residual volume (RV), total lung capacity (TLC) and functional residual capacity] measured by body plethysmography compared with control patients?
3. Does endobronchial valve placement in this group lead to a significant improvement in exercise capacity (endurance time at 70% of maximum workload) and dynamic hyperinflation measured during endurance cycle ergometry as isotime end-expiratory lung volume?
4. Does endobronchial valve placement lead to an improvement in walking distance assessed using the 6-minute walk test?
5. Does endobronchial valve placement in this group lead to a significant improvement in health-related quality of life?
6. Will the benefit seen in this group be of a magnitude likely to be sufficient to justify the cost of the procedure and the complications that occur?

Methods

The study was a double-blind, randomised, sham-controlled trial to investigate the effect of bronchoscopic lung volume reduction (BLVR) with endobronchial valves in patients with severe [Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage III and IV] heterogeneous emphysema and intact interlobar fissures.

Patients were recruited from the advanced COPD clinic at Royal Brompton Hospital. When clinically appropriate, patients had investigations including thoracic computerised tomography (CT) scans and pulmonary function tests to assess their eligibility for LVRS. All patients were discussed in a multidisciplinary meeting including a respiratory physician, radiologist and thoracic surgeon with additional physiotherapy and nursing input.

The inclusion criteria were as follows:

1. Adult patients with stable severe COPD (GOLD stage III or IV with FEV₁ < 50% predicted).
2. Medical Research Council (MRC) dyspnoea score between 3 and 5.
3. TLC > 100% predicted and RV > 150% predicted, assessed using body plethysmography.
4. 6-minute walk distance of < 450 m.
5. Patient on optimum medical therapy including inhaled corticosteroids and long-acting beta2-agonist and anticholinergic agents unless intolerant or declined to use them.
6. Thoracic CT scan demonstrating heterogeneous emphysema with a defined target lobe with lung destruction and intact adjacent interlobar fissures. Scans were reviewed by two radiologists independently and a third adjudicated on any disagreements. Radiologists agreed that the worst-affected lobe of the lung has an emphysema score of > 2 (according to the National Emphysema Treatment Trial scoring system), that it is at least 1 point higher than the ipsilateral lobes and that it has intact fissures visible on at least one projection.

The exclusion criteria were as follows:

1. significant comorbidity that limits exercise capacity or prognosis
2. significant daily sputum production
3. hypoxia [i.e. arterial oxygen tension (PaO₂) < 6.5 kPa while breathing air]
4. smoker.

All study participants underwent bronchoscopy performed using moderate sedation. Depending on their allocation patients had either unilateral lobar endobronchial valve placement aiming to achieve lobar atelectasis, or bronchoscopy and 'sham' valve placement. Although target lobe selection was based on CT appearances alone, measurements of collateral ventilation using the Chartis™ (Pulmonx, Palo Alto, CA, USA) balloon catheter system were carried out in all participants so that the accuracy of the two approaches could be compared.

At baseline and at 90 days, participants' health status was recorded and participants underwent a CT scan of the thorax, full pulmonary function tests, a 6-minute walk test and cycle ergometry at 70% baseline peak exercise capacity.

Results

The primary end point of the study was met as FEV₁ increased from baseline by a mean [95% confidence interval (CI)] of 24.8% (8.0% to 41.5%) in the treatment arm and 3.9% (0.7% to 7.1%) in the control arm, a between-group difference of 20.9% (4.3% to 37.5%; $p = 0.033$). This was associated with significant improvements in lung volumes, gas transfer and exercise capacity. Although differences in health status responses between groups were of a similar magnitude to the minimally clinically important differences, they were not statistically significant. No baseline parameter was associated with improvement in FEV₁.

Valve placement was associated with an improvement in endurance time on cycle ergometry (T_{lim}) [+139 seconds (95% CI 43 seconds to 235 seconds) vs. -2 seconds (95% CI -78 seconds to 73 seconds); $p = 0.021$] accompanied by reductions in dynamic hyperinflation. Improved T_{lim} was associated with improved FEV₁ and reduced respiratory rate and breathlessness at isotime.

There were two deaths in the treatment arm and two pneumothoraces, which responded to conventional treatment with intercostal tube drainage. One patient in the control arm was unable to attend the 90-day follow-up because of a prolonged air leak from a spontaneous pneumothorax.

Patients with collateral ventilation demonstrated by the Chartis system showed little benefit, suggesting that it has additional selective power even in individuals with apparently intact interlobar fissures on CT scan.

Conclusions

These findings confirm that in appropriately selected patients with emphysema (those with heterogeneous disease and intact interlobar fissures), endobronchial valve placement produces clinically significant improvements in lung function. Trials are needed to (1) compare BLVR directly with LVRS in terms of magnitude and duration of benefit as well as safety and (2) evaluate BLVR in specific groups such as patients with alpha-1 antitrypsin deficiency.

Trial registration

This trial is registered as ISRCTN04761234.

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