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

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Summary

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-centre, 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 a forced expiratory volume in 1 s (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 <450 m), and substantial breathlessness (MRC dyspnoea score ≥3). Participants were randomised (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 50 patients (62% male, FEV_1 [% predicted] mean 31·7% [SD 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 two deaths in the bronchoscopic lung volume reduction group and one 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.

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Introduction

Despite optimal pharmacological therapy and pulmonary rehabilitation, many patients with chronic obstructive pulmonary disease (COPD) remain very disabled.[1] In carefully selected patients with emphysema, lung volume reduction surgery (LVRS) to resect the worst affected areas of lung has improved lung function, exercise capacity health status, and survival.[2] However, this surgical intervention is associated with substantial morbidity, and an early mortality rate of about 5% was reported in the National Emphysema Treatment Trial (NETT) trial,[2] although recent case series have reported lower rates.[3] Nevertheless, there is still reluctance to refer patients for LVRS,[4] and there has been considerable interest in developing novel treatment approaches that can also reduce lung volumes and gas trapping, either more safely than LVRS, or else in patients for whom LVRS is not an option.[5–11]

One approach is placing endobronchial valves in the airways supplying the most emphysematous part of the lung using a fibreoptic bronchoscope (ie, bronchoscopic lung volume reduction, BLVR). The valves allow air to leave but not enter the target lobe, causing it to collapse and thus reducing gas trapping. In heterogeneous disease this reduction allows the relatively healthier lung to function better by diverting air to more perfused areas and recruiting previously compressed alveoli. Initial pilot work by our group and others was encouraging, showing that valve placement could

reduce dynamic hyperinflation, improving exercise capacity in association with improvements in inspiratory capacity and gas transfer.[7,10] Moreover, follow up of an early cohort showed that all patients in whom radiological atelectasis had occurred (n=5) were alive 6 years after the procedure, whereas eight of the 14 without radiological atelectasis had died[7] raising the possibility that BLVR might, like LVRS, offer a survival advantage in appropriately selected patients.

The VENT study compared unilateral endobronchial valve placement (n=220) with standard medical care (n=101).[5] The protocol did not mask the patients or assessors to the allocation of treatment and no sham procedures were done. The study showed statistically but not clinically significant mean differences in forced expiratory volume in 1 s (FEV_1; 6·85%) and 6 min walking distance (5·7%) between BLVR and control groups at 6 months. This small effect size was considered insufficient for Federal and Drug Administration approval. A post hoc analysis identified a subgroup of responders: patients with high heterogeneity and intact interlobar fissures who had a much bigger response with a mean 17·9% improvement in FEV_1 seen if fissures were intact compared with 2·8% if fissures were incomplete. Additionally, patients with the greatest degree of heterogeneity on CT had significantly greater improvement in both FEV_1 and 6 min walking distance.

Based on these data and evidence for a survival benefit where radiological atelectasis occurred,[7] we did a randomised, double-blind sham-controlled trial of endobronchial valve placement in patients with COPD (the Bronchoscopic Lung Volume Reduction for patients with Heterogeneous emphysema and Intact Fissures study [BeLieVeR-HIFi]). We hypothesised that valve placement would lead to a significant improvement in lung function, exercise capacity, and health status.

Methods

Study design and participants

The BeLieVeR-HIFi study was a randomised, parallel group, double-blind sham bronchoscopy controlled trial of unilateral, endobronchial valve placement (Zephyr valves; PulmonX, Redwood City, CA, USA) aimed to achieve lobar occlusion in patients with heterogeneous emphysema and intact interlobar fissures. Participants were recruited between March 1, 2012, and Sept 30, 2013.

We enrolled stable outpatients with COPD who met the following criteria: 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 <450 m) and substantial breathlessness (MRC dyspnoea score ≥3). Participants were all ex-smokers and on optimum medical therapy, including combined inhaled corticosteroids, long-acting β2 agonist, and anti-cholinergic agents unless they were intolerant or declined to use them. Patients were identified through a multidisciplinary COPD team meeting including chest physicians, surgeons, and radiologists. For inclusion, a CT scan of their thorax had to show 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 had to agree that the worst affected lobe of the lung had an emphysema score of more than 2 on the NETT study scoring system[2] and that it scored at least 1 point higher than ipsilateral lobes and had more than 90% intact oblique fissures visible.

	All (n=50)	BLVR (n=25)	Control (n=25)
Age (years)	62·8 (7·4)	62·3 (7·0)	63·3 (7·9)
Male (%)	31 (62%)	17 (68%)	14 (56%)
BMI (kg/m^2)	24·5 (4·8)	24·5 (5·1)	24·5 (4·6)
Pack year smoking history	54 (24)	56 (26)	51 (23)
Exacerbation rate per year	3 (3)	3 (3)	3 (2)
FEV_1 (L)	0·89 (0·32)	0·93 (0·35)	0·85 (0·30)
FEV_1 (% predicted)	31·7 (10·2)	31·6 (10·2)	31·8 (10·5)
TLC (% predicted)	137 (14)	132 (12)	143 (15)
Residual volume (% predicted)	232 (43)	219 (39)	245 (44)
RV/TLC (%)	62·14 (8·12)	60·23 (8·06)	64·06 (7·88)
TL_{co} (% predicted)	33·8 (9·9)	33·8 (10·8)	33·7 (9·0)
K_{co} (% predicted)	45·4 (12·1)	45·8 (12·8)	45·1 (11·7)
$PaCO_2$ (kPa)	4·85 (0·73)	4·81 (0·86)	4·90 (0·61)
PaO_2 (kPa)	9·60 (1·20)	9·74 (1·45)	9·47 (0·89)
MRC dyspnoea score	4 (1)	4 (1)	4 (1)
CAT	25 (5)	24 (5)	27 (5)
SGRQc (symptoms)	71·23 (16·29)	68·49 (15·78)	73·97 (16·65)
SGRQc (activity)	88·35 (11·86)	86·41 (13·51)	90·29 (9·85)
SGRQc (impact)	57·14 (16·26)	56·47 (16·92)	57·81 (15·89)
SGRQc (total)	69·22 (12·78)	67·79 (13·17)	70·65 (12·48)
6MWD (m)	338 (87)	342 (94)	334 (81)
Peak workload (W)	23	25	21
Peak VO_2 (L/min)	0·89	0·93	0·86
Peak VCO_2 (L/min)	0·84	0·90	0·77
Peak VE (L/min)	41·12 (12·76)	41·84 (12·58)	40·40 (13·15)
Peak VE (% predicted)	41	42	40
T_{LIM} (s)	305 (169)	306 (166)	305 (175)

Data are n (%) or mean (SD). BLVR=bronchoscopic lung volume reduction. BMI=body-mass index. FEV_1=forced expiratory volume in 1 s. TLC=total lung capacity. RV=residual volume. TL_{co}=carbon monoxide transfer factor. K_{co}=carbon monoxide transfer coefficient. $PaCO_2$=arterial partial pressure of CO_2. PaO_2=arterial partial pressure of O_2. MRC=Medical Research Council. CAT=chronic obstructive pulmonary disease (COPD) assessment test score. SGRQc=St George's respiratory questionnaire for COPD. 6MWD=6 min walking distance. Workload=results of incremental cycle ergometry. VO_2=oxygen consumption. VCO_2=CO_2 production. VE=minute ventilation. T_{LIM}=endurance time on cycle ergometry at 70% of peak workload.

Table 1: **Baseline characteristics of study participants**

Patients were excluded if they had substantial comorbidity restricting their exercise capacity or prognosis; substantial daily sputum production; or hypoxia (ie, PaO_2 <6·5 Pa breathing air). Lower limits for lung function were not otherwise formally defined but patients were excluded if they were considered clinically to be too restricted or frail to undergo bronchoscopy or to tolerate a pneumothorax.

The study was approved by the London—Bentham Research Ethics Committee (REC number 11/LO/1608); the sponsor was Imperial College, London. There was a trial steering group and an independent data monitoring committee. All patients provided written informed consent.

Randomisation and masking

We randomly assigned patients (1:1) to either BLVR or control groups using predetermined block randomisation, with a block size of 10, computer-generated by the trial statistician (WB). The allocation was obtained by telephone link from the bronchoscopy suite to the Clinical Trials Unit at the Royal Brompton Hospital once the patient had been sedated. Masking was maintained by having two separate teams: one which undertook the randomised procedures (PLS, ZZ, WHM) and a separate team, masked to study assignment, responsible for recruitment and the assessments (CD, MIP, NSH), as previously used in trials of bronchoscopic therapies for emphysema.[10] Thus, both patients and the researchers assessing outcomes were masked to treatment allocation.

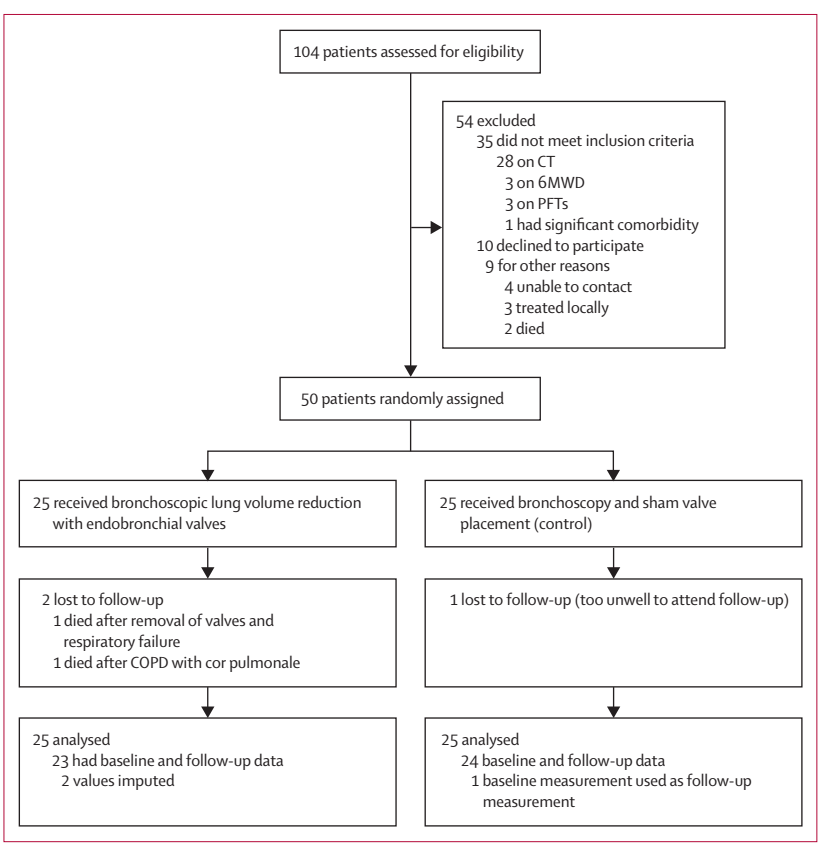

Figure 1: **Trial profile**
6MWD=6 min walking distance. PFTs=pulmonary function tests. COPD=chronic obstructive pulmonary disease.

Procedures

The procedures took place within 2 weeks of the baseline assessment visit. Study participants underwent either unilateral lobar endobronchial valve placement aiming to achieve lobar atelectasis (BLVR group), or bronchoscopy and sham valve placement (control group). All procedures were done in the bronchoscopy suite at the Royal Brompton Hospital using moderate sedation with midazolam and alfentanyl. Procedures were done by a single operator (PLS) with an expertise in interventional bronchoscopy who had done more than 50 endobronchial valve procedures before study commencement.

Although target lobe selection was based on CT appearance alone, measurements of collateral ventilation using the Chartis (PulmonX, Redwood City, CA, USA) balloon catheter system were made in all participants so that the accuracy of the two approaches could be compared.[12] Endobronchial valves were placed to occlude segmental bronchi leading to the target lobe (irrespective of the Chartis results). All procedures were unilateral. All patients underwent a chest radiograph after the procedure to check for the presence of a pneumothorax, which was reviewed by the treatment team only. If this was satisfactory they were then discharged home. Patients were counselled and provided with a post-procedure information sheet, irrespective of treatment allocation, giving advice on seeking medical attention in the presence of chest pain or sudden breathlessness, and providing advice for medical staff if the patient presented as an emergency.

Baseline and 3 month follow-up visits were done by an assessment team masked to treatment allocation. Spirometry, gas transfer, and lung volumes assessed by body plethysmography were measured with a CompactLab system (Jaeger, Hoechberg, Germany).[13] Lung function tests were all done after bronchodilator use. Predicted values used were those of the European Coal and Steel Community.[14,15] Patients underwent endurance cycle ergometry with metabolic measurements at 70% of their maximum workload determined on an initial incremental test. Inspiratory capacity manoeuvres were done to track changes in dynamic hyperinflation assessed as end-expiratory lung volume. Patients also completed a 6 min walking test done according to American Thoracic Society guidelines on a 30 m course.[16] Health-related quality of life was assessed using the St George's respiratory questionnaire for COPD (SGRQc)[17] and COPD assessment test (CAT).[18,19] Target lobe volume change was assessed by a radiologist (DHC) as an explicatory variable and scored as follows: 0, no change; 1, some volume loss (fissures shift); 2, segmental atelectasis (band of collapsed lung); 3, complete atelectasis (complete collapse).

Outcomes

The primary endpoint was the between group difference in the percentage change in FEV_1 measured 3 months after the procedure. Secondary endpoints were: change in endurance time (T_{LIM}) on cycle ergometry at 70% of maximum achieved workload and changes in end expiratory lung volume at isotime; change in 6 min walking distance; and changes in health status (scores on the CAT and SGRQc).

Statistical analysis

Sample size calculation was based on the results in the VENT study subgroup in which complete lobar occlusion was achieved.[5] This group had a mean 20·6% (SD 25·1) improvement in FEV_1 at 6 months compared with a 2·5% (2·5) fall in the control group. We considered an absolute difference in response between the two groups of 15% to be clinically significant. An 80% power and a significance level of 0·05 needed 21 patients in each group assuming that the mean change in FEV_1 from baseline in the control group was 0% (2·5) and the mean change in the group receiving BLVR was 15% (25). 50 patients were recruited to allow a 20% drop-out rate.

Data were entered into an electronic database developed by The Imperial College Clinical Trials Unit using InForm (Oracle, Reading, UK), and analysis was done by the trial statistician (WB) using Stata version 12 and SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). Analysis was on an intention-to-treat basis as pre-specified in a formal statistical analysis plan. Categorical data are presented as percentages and comparisons done using the Pearson χ^2 test. Normally distributed numeric data are presented as mean with SD or 95% CI. Non-normally distributed numeric data are presented as median (IQR). Because responses were skewed, Mann-Whitney testing was used to test whether the response to BLVR treatment was better than placebo. A post hoc univariate analysis of factors associated with change in cycle endurance time using regression with cluster option (ie, taking into account the paired nature of the data and relaxing the conditions for independence) was done. A p value of less than 0·05 indicated statistical significance. Missing data were imputed using the Markov chain Monte Carlo method, which creates multiple imputations by using simulations from a Bayesian prediction distribution. For responder analyses, minimum clinically important differences were pre-specified as a 15% increase for FEV_1, 350 mL reduction in the residual volume,[20] 4 point decrease on the SGRQc scale,[17,21] 2 point decrease on the CAT scale,[19,22] an increase of 105 s for endurance cycle T_{LIM},[23] and an increase of 26 m in 6 min walking distance.[24] The trial is registered at controlled-trials.com, ISRCTN04761234. The protocol has been published elsewhere.[25]

	BLVR	Control	p value
ΔFEV_1 (%)	8·77% (2·27 to 35·85)	2·88% (0 to 8·51)	0·0326
ΔFEV_1 (L)	0·06 (0·02 to 0·38)	0·03 (0 to 0·06)	0·0273
ΔVC (%)	3·75% (–1·02 to 9·95)	0·84% (–7·14 to 6·57)	0·1370
ΔFEV_1/VC	6·60 (2·61 to 23·04)	0·75 (–4·96 to 9·52)	0·0293
ΔTLC (%)	–3·38% (–7·88 to 1·05)	–1·57% (–3·09 to 0·89)	0·0448
ΔTLC (L)	–0·32 (–0·70 to –0·06)	–0·10 (–0·24 to –0·00)	0·0603
ΔRV (%)	–6·58% (–18·60 to 2·94)	–2·06% (–6·51 to 1·24)	0·0592
ΔRV (L)	–0·26 (–1·07 to –0·16)	–0·08 (–0·39 to –0·08)	0·0798
ΔRV/TLC	–3·95 (–8·32 to 0·66)	–1·20 (–2·46 to 1·28)	0·0715
ΔFRC (%)	–5·81% (–15·71 to 0·89)	0·97% (–2·25 to 3·31)	0·0119
ΔFRC (L)	–0·24 (–1·14 to 0·06)	0·07 (–0·15 to 0·20)	0·0213
ΔTL_{co} (mmol/min per kPa)	0·30 (0·03 to 0·43)	0 (–0·19 to 0·13)	0·0029
ΔK_{co} (mmol/min per kPa per L)	0·05 (0·01 to 0·11)	0·01 (–0·03 to 0·06)	0·0130
ΔMRC dyspnoea score	0 (–1 to 0)	0 (–1 to 0)	0·4037
ΔCAT (points)	–2 (–7 to 3)	0 (–2 to 2)	0·2269
ΔSGRQc total (points)	–4·40 (–16·93 to 6·76)	–3·57 (–7·67 to 2·55)	0·3454
Δ6MWD (m)	25 (7 to 64)	3 (–14 to 20)	0·0119

Data are median (IQR). p values are for Mann-Whitney test. BLVR=bronchoscopic lung volume reduction. FEV_1=forced expiratory volume in 1 s. VC=vital capacity. TLC=total lung capacity. RV=residual volume. FRC=functional residual capacity. TL_{co}=carbon monoxide transfer factor. K_{co}=carbon monoxide transfer coefficient. CAT=chronic obstructive pulmonary disease (COPD) assessment test score. SQRGc=St George's respiratory questionnaire for COPD. 6MWD=6 min walking distance.

Table 2: **Change in outcome measures from baseline to 3 months**

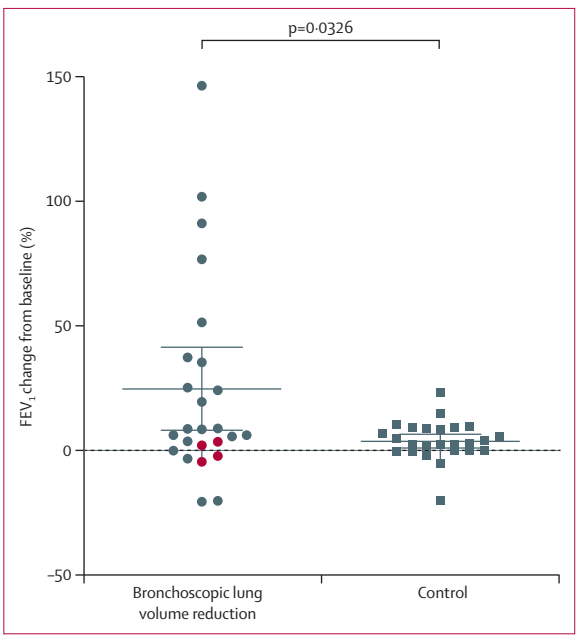

Figure 2: **Change in forced expiratory volume in 1 s (FEV_1) at 3 months in patients treated with bronchoscopic lung volume reduction with endobronchial valves compared with controls who underwent sham treatment**
Bars are mean and 95% CIs. Red symbols represent the four patients who had collateral ventilation detected using the Chartis system and were treated with bronchoscopic lung volume reduction.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

See Online for appendix

The baseline characteristics of the 50 enrolled patients with COPD are shown in table 1 and more fully in the appendix. BLVR and control groups were generally well matched, but percent predicted residual volume and total lung capacity were higher in the control group. The trial profile describing patient flow through the study is shown in figure 1. The median number of valves placed per patient was 3 (range 1–6). There were two deaths in the BLVR group and one control patient was unable to attend for follow-up assessment because of a prolonged pneumothorax; 3 month data were available for 23 patients receiving BLVR and 24 controls.

	BLVR	Control	p value
T_{LIM} (s)	25 (–53 to 302)	–10·8 (–69 to 33)	0·0256
Isotime			
EELV (L)	–0·35 (–1·16 to –0·07)	0·01 (–0·27 to 0·26)	0·0060
IRV (L)	0·04 (–0·04 to 0·25)	–0·09 (–0·38 to 0·14)	0·0434
VE (L/min)	0·14 (–2·45 to 2·83)	0·83 (–1·76 to 2·76)	0·4074
RR (/min)	0 (–10 to 1)	0 (–2 to 4)	0·1223
V_t (mL)	32·60 (25·96 to 40·30)	27·29 (22·28 to 33·66)	0·0369
Borg leg discomfort	0 (–1 to 1)	0 (–1 to 1)	0·2692
Borg breathlessness	0 (–2 to 0)	0 (–1 to 2)	0·0800
Peak			
EELV (L)	–0·33 (–1·06 to –0·04)	–0·01 (–0·26 to 0·19)	0·0059
IRV (L)	0·09 (–0·09 to 0·35)	–0·085 (–0·315 to 0·115)	0·0233
VE (L/min)	–0·18 (–2·16 to 5·23)	–0·55 (–1·93 to 2·84)	0·4577
RR (/min)	–1 (–5 to 2)	–1 (–3 to 4)	0·1478
V_t (mL)	33·82 (26·48 to 40·28)	28·05 (22·25 to 35·29)	0·0306
Borg leg discomfort	0 (–1 to 1)	0 (–1 to 0)	0·3086
Borg breathlessness	0 (–1 to 1)	0 (–1 to 1)	0·4451

Data are median (IQR). p values are for Mann-Whitney test. BLVR=bronchoscopic lung volume reduction. T_{LIM}=endurance time at 70% peak workload. EELV=end expiratory lung volume. IRV=inspiratory reserve volume. VE=minute ventilation. RR=respiratory rate. V_t=tidal volume.

Table 3: **Change in exercise variables from baseline to 3 month follow-up**

	Univariate regression			Multiple stepwise regression		
	β (95% CI)	r^2	p value	β (95% CI)	r^2	p value
ΔFEV_1	7·18 (2·29 to 12·07)	0·60	0·005	3·24 (1·64 to 4·85)		<0·0001
ΔVC	3·97 (1·03 to 6·90)	0·60	0·009	..	..	..
ΔTL_{CO}	2·76 (0·88 to 4·64)	0·57	0·005	..	..	..
ΔTLC	–1·84 (–3·98 to 0·30)	0·54	0·090	..	..	..
ΔRV	–2·83 (–4·55 to –1·10)	0·61	0·002	..	..	..
ΔIC (at rest)	4·32 (1·92 to 6·73)	0·62	0·001	..	..	..
ΔEELV (isotime)	–2·50 (–3·88 to –1·12)	0·61	0·001	..	..	..
ΔIRV (isotime)	3·97 (0·63 to 7·32)	0·57	0·021	..	..	..
ΔV_T (isotime)	8·06 (1·43 to 14·68)	0·60	0·018	..	..	..
ΔRR (isotime)	–0·29 (–0·45 to –0·14)	0·63	0·000	–0·07 (–0·14 to –0·006)	0·59	0·033
ΔBorg dyspnoea score (isotime)	–0·69 (–1·08 to 0·30)	0·58	0·001	–0·26 (–0·49 to –0·02)	..	0·032
ΔBorg leg discomfort score (isotime)	–0·04 (–0·60 to 0·68)	0·51	0·90	..	..	..

Univariate analysis of factors associated with change in cycle endurance time using regression with cluster option (ie, taking into account the paired nature of the data and relaxing the conditions for independence). Factors with a p<0·05 in univariate analysis were entered into multiple regression analysis. ΔFEV_1, ΔRR (isotime), and ΔBorg dyspnoea score (isotime) explained 59% of the variance in change in cycle endurance time. FEV_1=forced expiratory volume in 1 s. VC=vital capacity. TL_{CO}=carbon monoxide transfer factor. TLC=total lung capacity. RV=residual volume. IC=inspiratory capacity. EELV=end expiratory lung volume. IRV=inspiratory reserve volume. V_t=tidal volume. RR=respiratory rate.

Table 4: **Factors associated with change in cycle endurance time at 3 months**

Response to treatment was assessed at 3 months (mean [SD] 93 [12] days; table 2, figure 2, and appendix). FEV_1 increased by a mean 24·8% (95% CI 8·0–41·5) from baseline in the BLVR group and 3·9% (0·7–7·1) in controls. However, the response in the BLVR group was heavily skewed so non-parametric tests were used for analysis. Median (IQR) FEV_1 changes at 3 months were 8·77% (2·27–35·85) in the BLVR group and 2·88% (0–8·51) in controls (Mann-Whitney p=0·0326; table 2). The BLVR group also had a significant improvement in 6 min walking distance and T_{LIM} on cycle ergometry (tables 2 and 3). This result was accompanied by significant improvements in lung volumes and gas transfer. CAT and SGRQc scores improved more in the BLVR group but compared with the control group were not statistically significant. Improvement in FEV_1 was not associated with any baseline variable (appendix).

In univariate analysis, improvement in cycle ergometry T_{LIM} was associated with improvements in spirometry, lung volumes, and gas transfer, and reductions in dynamic lung volumes, respiratory rate, and breathlessness during exercise (table 4). In multivariate analysis, an increase in FEV_1 was retained, together with a fall in isotime respiratory rate and Borg dyspnoea score, as factors associated with improvement in T_{LIM} (r^2=0·59, p<0·0001). In the BLVR group, eight patients were scored as having "complete collapse" of the target lobe, five "a band of atelectasis", two "some volume loss", and eight no change.

Four treated patients, despite having fissures scored as intact on CT as a criterion for study entry, had collateral ventilation detected by the Chartis system (collateral ventilation positive). Table 5 compares response rates between controls and the whole BLVR group and the BLVR group with collateral ventilation positive patients excluded. Of note, it was not possible to determine collateral ventilation in six (12%) patients with the Chartis system, consistent with a previous study reporting a 7% failure rate.[26]

Individual patient responses to treatment are shown in the appendix, including both absolute values and numbers achieving the minimum clinically important differences for the various variables measured. These data also show the lobe targeted and whether collateral ventilation was detected by the Chartis system.

Two patients in the BLVR group died within 90 days of the procedure (table 6). The first developed a cough and a decision was taken to remove the valves 49 days after they had been placed. At the time of removal, which was difficult, he developed a tension pneumothorax with an ongoing significant air leak. He progressed to respiratory

	BLVR		Control (n=24)	p value*
	All (n=23)	CV-positive excluded (n=19)		
FEV_1	9 (39%)	..	1 (4%)	0·0044
>15% improvement	..	9 (47%)	1 (4%)	0·0022
RV	11 (48%)	..	7 (29%)	0·24
0·35 L reduction[20]	..	11 (58%)	7 (29%)	0·07
6MWD	12 (52%)	..	4 (17%)	0·012
26 m improvement[24]	..	12 (63%)	4 (17%)	0·004
Endurance cycle time	10 (43%)	..	2 (8%)	0·008
105 s improvement[23]	..	9 (47%)	2 (8%)	0·005
SGRQc	11 (48%)	..	11 (46%)	1·0
4 points reduction[21]	..	11 (58%)	11 (46%)	0·5
CAT	13 (57%)	..	7 (29%)	0·080
2 points reduction[22]	..	13 (68%)	7 (29%)	0·015

Data are n (%). CV-positive=collateral ventilation using Chartis system. BLVR=bronchoscopic lung volume reduction. FEV_1=forced expiratory volume in 1 s. RV=residual volume. 6MWD=6 min walking distance. SGRQc=St George's respiratory questionnaire for chronic obstructive pulmonary disease (COPD). CAT=COPD assessment test score. *Fisher's exact test (this analysis does not include imputed values).

Table 5: **Responder rates according to lung function, health status, and exercise criteria**

	BLVR (n=25)		Control (n=25)		p value
	Events	Patients	Events	Patients	
Exacerbation (total)	23	16	22	20	0·42*, 0·35†
Of which required hospitalisation	5	..	3	..	0·70
Pneumonia (respiratory tract infection with radiograph changes)	2	2	0	0	0·49
Pneumothorax	2	2	1	1	1·0
Deaths	2	..	0	..	0·49
Respiratory failure	1	..	0	..	1·0
COPD with cor pulmonale	1	..	0	..	1·0
Expectorated valve	5	4	0	0	..
Removal of valves	2	2	0	0	..
Seizure (unrelated)	0	0	1	1	1·0

p value is for χ^2 test. BLVR=bronchoscopic lung volume reduction. COPD=chronic obstructive pulmonary disease. *Comparison of patients. †Comparison of events.

Table 6: **Adverse events**

failure, dying 17 days later despite intensive care treatment including endotracheal tube intubation and use of arteriovenous extracorporeal CO_2 removal. The second patient died suddenly 3 days after valve placement. He underwent a post mortem; there was no evidence of pneumonia or pneumothorax and a diagnosis of death due to COPD with cor pulmonale was made. One patient in the control group was too unwell to attend for follow-up because of a spontaneous pneumothorax with prolonged air leak with onset 66 days after his sham bronchoscopy. Additionally, two patients in the BLVR group had pneumothoraces which both responded to intercostal tube drainage, one at 3 days and one at 12 days after the procedure. Four patients expectorated a valve before 3 months. These were replaced in three of four individuals before their follow-up visit. The patients were instructed not to inform the assessment team of these additional procedures.

Discussion

Placement of endobronchial valves in patients with severe COPD who have heterogeneous emphysema and intact interlobar fissures on CT scan was associated with improvements in lung function and exercise capacity. This prospective, double-blind, randomised, controlled trial is the first study of bronchoscopic treatment to achieve this, through the use of an appropriately stratified approach to target a responder emphysema phenotype (panel). Our data suggest that in appropriately selected patients, endobronchial valve placement results in improvements in lung function which are of a similar order of magnitude to those seen with LVRS.[2,3,27] The improvement in gas transfer is important because this is the lung function variable most strongly associated with survival in people with COPD.[13] Previous trials such as VENT included many patients with collateral ventilation who therefore derived less benefit, in particular less lobar atelectasis, which is a key determinant of effectiveness associated with improved lung function response[5,8] and survival.[7] Prospectively stratifying in favour of patients with heterogeneous disease and radiologically intact fissures substantially increased the response rate.

The success rate of valve placement was higher than in previous studies because only patients with intact interlobar fissures on CT were included; however, there were cases of positive collateral ventilation when assessed using the Chartis system. These cases were associated with no benefit from treatment raising the possibility of an additive role in improving patient selection. The Chartis system adds cost and time to procedures and its use cannot necessarily be recommended based on the present data. Furthermore, satisfactory Chartis measurements were not always possible for technical reasons (about 10%), a finding consistent with previous studies.[26] We acknowledge that the positive and negative predictive power of collateral ventilation measured with the Chartis system will vary depending on the CT criteria and method of fissure analysis used in the initial selection strategy because this will affect the pre-test probability of collateral ventilation. The ideal strategy for selecting patients in whom lobar exclusion can be achieved needs to be defined and will remain unclear as refinements in technology and CT scoring of fissure integrity evolve.

A key issue is the safety of this treatment approach. Spontaneous pneumothorax can occur when valve placement leads to a change in the conformation of the lung and can be a marker of effective lobar occlusion. Therefore, as patient selection improves an increase in the

Panel: Research in context

Systematic review

Interest has grown in mechanical lung volume reduction approaches for patients with emphysema and a variety of bronchoscopic techniques are in development. The most widely studied bronchoscopic approach is endobronchial valves. We searched PubMed using the terms "emphysema", "chronic obstructive pulmonary disease", "endobronchial valves", and "bronchoscopic lung volume reduction", without restrictions on language or article type up until May 1, 2014, to identify any case reports, case series, and clinical trials of endobronchial valves for the treatment of emphysema. We identified only two randomised controlled trials that used a unilateral complete lobar occlusion approach, randomising a combined 416 patients to either an unmasked bronchoscopic procedure with valve implantation or to best medical care (no sham bronchoscopy). These studies showed the safety of endobronchial valves, but average benefits were modest. In some patients there were dramatic improvements, in others no response. Retrospective analysis has suggested a responder phenotype with heterogeneous emphysema and intact interlobar fissures identified on CT. In this UK National Institute for Health Research funded (and thus independent of industry) study, we sought to establish whether targeting patients with heterogeneous emphysema and intact interlobar fissures on CT could improve outcomes. It is the first double-blind randomised sham-controlled trial of endobronchial valves.

Interpretation

Placing endobronchial valves to completely occlude the most diseased lobe in patients with heterogeneous emphysema and intact fissures assessed using CT results in significant improvements in lung function and exercise capacity.

pneumothorax rate is inevitable. In the present study pneumothorax occurred in two treated patients (8%) and in one control patient (4%). The management of pneumothorax in this context is conventional, usually with intercostal tube drainage. However, it is important that patients are selected who are considered likely to be able to withstand the associated acute lung function impairment a pneumothorax will cause. In part, bronchoscopic treatment for emphysema has been developed for people considered to be too disabled to withstand LVRS, but caution is needed given the pneumothorax risk. There were two deaths in the BLVR group. One occurred as a complication of valve removal, which was difficult. Therefore, if valves need to be removed this should be done with limited force and if the valve cannot be removed easily a more controlled approach via rigid bronchoscopy should be considered. A rigid bronchoscopy approach might also be appropriate where there is significant granulation tissue or where the valve is at an acute angle. Because rigid bronchoscopy tends to be done by surgeons rather than physicians, this emphasises the importance of close liaison with thoracic surgery in the approach to the management of these patients.

A strength of the study was the masking of patients and assessors. The presence of a sham bronchoscopy meant that a more confident estimate could be made of changes in health status that have often been large in unmasked studies, even in the absence of significant changes in lung function.[28] The assessment of collateral ventilation in all participants using the Chartis system meant that control patients also underwent a procedure, which reinforced masking. Although patients in whom a pneumothorax occurred or who expectorated a valve were unmasked, valves are difficult to visualise on chest radiographs and this maintained masking of physicians and patients alike if they underwent investigations for a clinical deterioration in the absence of a pneumothorax.

The study was undertaken at a single centre with experience in bronchoscopic procedures and in selecting patients for lung volume reduction. Therefore, it shows the results that are possible. However, for these results to be generalisable, it will require the establishment of a similar clinical infrastructure, and as with any new technique, there is likely to be a learning curve as it is implemented.

In some patients, ideal positioning of the valves is not possible due to patient anatomy (eg, insufficient length of bronchus to place the valve adequately leading to early expectoration, or difficult access to a particular segment), which might affect the effectiveness of valves as a treatment strategy. The present study was not sufficiently large for this to be an issue but we recommend in future studies that a bronchoscopic assessment of the technical feasibility of valve placement be included in the protocol. It remains the case that LVRS is an effective treatment in upper lobe predominant bullous emphysema regardless of fissure integrity.

Further work is needed to establish how this technique should best be deployed relative to LVRS[2,3] and other developing techniques, such as lung volume reduction coils[9] and bronchoscopic thermal vapour ablation.[29] Most importantly, there is a considerable overlap between the indications for BLVR and LVRS, and thus a stepwise approach with bronchoscopic techniques considered at an earlier stage to defer, prevent, or act as a bridge to LVRS could be appropriate. Alternatively, LVRS might be the definitive treatment that should be offered earlier. Prospective trials comparing LVRS and valve placement will be needed to clarify this.

Contributors

NSH, MIP, SJ, DMH, and PLS developed the study. NSH, MIP, SJ, DHC, MBR, and DMH were involved in patient selection. PLS, ZZ, and WHM did the procedures. CD did the assessments. WB, with NSH and CD, developed the statistical analysis plan and did the analyses. NSH, ZZ, and CD prepared the first draft of the manuscript, which all authors subsequently contributed to and approved. NSH is the guarantor.

Declaration of interests

PLS, SJ, MIP, ZZ, WHM, and NSH have been investigators in trials of endobronchial valves, coils, thermal ablation, and the airway bypass procedure, and the authors' institution was reimbursed for trial expenses by the device manufacturers. NSH reports non-financial support from Pulmonx, during the conduct of the study. ERBE, Cook Medical, Superdimension, Boston Scientific, Aquilant, Broncus, Pulmonx, Olympus, and PneumRX have sponsored an interventional bronchoscopy course that PLS organises through Imperial College. The other authors declare no competing interests.

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