

Radiological and Clinical Outcomes of Using Chartis to Plan Endobronchial Valve Treatment

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Abstract

Background: One-way endobronchial valves (EBV) have been shown to relieve symptoms of emphysema, particularly in patients without collateral ventilation (CV) between the target and adjacent lobes. In this study, we investigated the ability of the bronchoscopic Chartis Pulmonary Assessment System™ to predict treatment response by determining the presence of CV.

Methods: EBV patients (n = 80) underwent a pre-treatment Chartis assessment. Before and 30 days after implantation, high-resolution CT scans were taken to determine target lobe volume reduction (TLVR). A pre- to post-treatment reduction of ≥ 350 ml was defined as significant. In addition, clinical outcomes (FEV₁, 6-minute walk test and SGRQ) were compared over the same time period.

Results: Of the 51 patients classified as having an absence of CV according to their Chartis reading, 36 showed a TLVR ≥ 350 ml. Twenty-nine patients were classified as having CV, and of these 24 did not meet this TLVR cut-off. Chartis showed an accuracy level of 75% in predicting whether or not the TLVR cut-off would be reached. Those predicted to respond showed significantly greater TLVR ($p < 0.0001$) and FEV₁ improvement ($p = 0.0013$) than those predicted not to respond.

Conclusion: Chartis is a safe and effective method of predicting response to EBV treatment.

Keywords: Chronic obstructive pulmonary disease, collateral ventilation, emphysema, endoscopic lung volume reduction

Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the world, and is expected to be so until at least the year 2030 [1].

Emphysema is a component of COPD, and is present in approximately 1.8% of the global population [2].

Emphysema is a progressive debilitating disease characterised by irreversible destruction of alveolar tissue. This results in reduced elastic recoil, progressive hyperinflation and gas trapping [3, 4]. Patients experience chronic dyspnoea, limited exercise tolerance and poor quality of life (QoL) [5].

Patients with severe emphysema remain significantly disabled despite treatment with pulmonary rehabilitation [6], optimum medical therapy [7] and long-term supplemental oxygen [8]. These therapies are not able to reverse or remove the hyperinflation caused by the alveolar destruction, and therefore provide limited benefit.

Lung volume reduction surgery (LVRS) involves the resection of areas of diseased lung to reduce hyperinflation and improve breathing mechanics. The NETT Study [5, 7] demonstrated that this procedure can provide clinical benefit to selected patient groups: those with predominantly upper lobe disease and low exercise capacity. However, this procedure is associated with significant morbidity and mortality. It has been reported to have a three-month postoperative mortality rate of 5–10% and a nonfatal complication rate of 60% [5].

Endobronchial valves (EBV) are one-way valves designed to be placed in the bronchi to allow air and secretions to escape the lobe, but no further air to re-enter. As a result (partial) atelectasis of the treated lobe develops, and the lung volume is reduced, with associated clinical improvement.

The Endobronchial Valve for Emphysema Palliation Trial (VENT Study) [9, 10] was the first randomised controlled study to assess the effectiveness of EBV (Zephyr® EBV, Emphasys Medical, now Pulmonx Inc., Redwood, CA, USA). Both the US [9] and European [10] cohorts showed modest improvements in lung function,

exercise tolerance and QoL compared to controls. However, subgroup analyses performed on both sets of data revealed that the degree of lung volume reduction and the associated clinical improvements were far more pronounced in the patients showing complete fissures on CT and where EBV placement had resulted in complete lobar occlusion. It is considered that collateral ventilation (CV) into the target lobe from the adjacent lobe(s) through collateral channels is the key reason why, in some cases, lung volume reduction is not achieved with EBV. The presence of complete fissures on CT between the target and adjacent lobes suggests an absence of CV to the target lobe [9, 11]. Therefore, assessment of CV prior to intervention could help in the planning of EBV placement into lobes without CV, hence maximising clinical benefit.

The Chartis Pulmonary Assessment System™ [12] consists of a single-patient-use catheter with a compliant balloon component at the distal tip, which upon inflation blocks the airway. Air can then flow out from the target compartment into the environment only through the Chartis catheter's central lumen. By connecting to a Chartis console, airway flow and pressure can be displayed. Airway resistance can be calculated and CV in isolated lung compartments can be measured.

The objective of this study was to determine whether Chartis assessment of CV can predict whether EBV placement results in significant target lobe volume reduction (TLVR) for individual patients. Common clinical outcomes were also assessed.

Materials and Methods

Patients

From March 2010 to March 2011, patients considered appropriate candidates for an EBV placement were recruited from five clinics: three in Germany, one in The Netherlands and one in Sweden. None of these sites were participating in other trials that could have caused any bias in patient selection for this study. There was an enrolment limitation stating that only a maximum of 50% of patients from each site could be predicted non-responders to EBV treatment

(i.e. patients in whom CV was present); however, this limit was never reached, so no patients were excluded as a result. All participants had to provide written informed consent. Ethics committee approval was obtained from each of the participating centres. This study was registered at clinical trials.gov (NCT01101958).

Patients included were aged ≥ 18 years and had a diagnosis of late-stage heterogeneous emphysema (as assessed by visual read only of a CT scan by the investigator).

Those with an active pulmonary infection, a forced expiratory volume (FEV₁) < 15 or $> 50\%$ of the predicted value, any coexisting medical problem that would contraindicate a bronchoscopic procedure, or who were participating in a trial on an investigational drug or device were excluded.

In order to obtain a sample of patients that was representative of daily clinical practice, these were the only criteria used for patient enrolment.

Study Design

This was a non-randomised multicentre prospective study. The primary objective of the study was to evaluate the effectiveness of Chartis in selecting patients who would benefit from EBV therapy. The primary outcome measure was the TLVR achieved.

Firstly, based upon visual read of the high-resolution CT (HRCT) scan, the lobe with the greatest destruction resulting from emphysema was identified by the study investigator in each centre. This was considered the target lobe for EBV treatment. In the rare event of bilateral disease of equal severity on HRCT, designation of the target lobe was left to the clinical judgment of the investigator.

Then, prior to EBV placement, the pre-designated target lobe was assessed using Chartis to determine the presence (CV+) or absence (CV-) of CV. Regardless of these results, the choice of target lobe remained the same. The EBV were then placed in segmental or lobar bronchi, with the aim of achieving complete lobar occlusion.

Finally, at the 30-day follow-up, another HRCT scan was taken and used in conjunction with the pre-treatment scan to determine the TLVR by a blinded core laboratory.

Before commencing the study, the investigators and core laboratory agreed that a ≥ 350 ml TLVR would be considered significant. This was on the basis that in the VENT study [9] the maximum TLVR in the control group ($n = 101$; receiving standard medical care) rarely exceeded this level. Moreover, using the same data, estimates of sensitivity and specificity pairs showed that the ideal TLVR threshold associated with FEV₁ response was between 300 and 400 ml (Pulmonx, unpublished data). A subsequent ROC analysis found TLVR to be a significant predictor ($p < 0.0001$) of FEV₁ response at 12 months (Pulmonx, unpublished data). Based on the average lung volumes recorded in the Chartis feasibility study (1,800 ml) [11] and the VENT study (1,700 ml), a ≥ 350 ml TLVR is equivalent to approximately a 20% reduction in lung volume.

In addition, patients were requested to complete Pulmonary function tests, the 6-minute walk test (6MWT) and the St. George's Respiratory Questionnaire (SGRQ) before and 30 days after the procedure.

For the responder analyses, those predicted to respond (CV_{-all}) or not (CV_{+all}) were broken down into responders ($CV_{-responders}$, $CV_{+responders}$) and non-responders ($CV_{-non-responders}$, $CV_{+non-responders}$). A responder was defined as a patient who obtained a ≥ 350 ml TLVR regardless of CV status.

Methods of Treatment

Chartis Assessment System

Chartis has two components: (1) A balloon catheter that is inserted via the working channel of the bronchoscope. Inflation of the balloon occludes the airway, blocking the flow of inspired air and allowing air to flow out only through the central lumen of the catheter. (2) A console to display the flow and pressure readings in real time. If there is no CV to feed the airway distal to the balloon, air flow out of the lobe will gradually reduce. A continuous flow reading indicates the presence of CV in the target lobe.

Zephyr Endobronchial Valve

The Zephyr one-way EBV has been designed to effectively block airflow into the target lung region whilst allowing air and secretions to leave [13]. The silicone valve is attached to a nickel-titanium (nitinol) self-expanding retainer that expands to fit the bronchial lumen without leakage from the retainer edges. If necessary, it can be removed [13].

Methods of Assessment

Radiographic Measures

Multi-row detector HRCT scans were taken before and 30 days following the procedure. These were read and analysed by a blinded core laboratory. TLVR was determined as previously reported [9, 14].

Heterogeneity of emphysema was determined using a semi-automated computer-based quantitative analysis of HRCT scans, as described previously [9, 10].

Clinical Measures

The following clinical outcomes were assessed in each of the patients before treatment and at the 30-day follow-up: FEV₁, 6MWT and SGRO.

Statistical Analysis

Radiographic Measures

Patients with a ≥ 350 ml TLVR were defined as having shown significant improvement over baseline values. For between-group comparisons, the TLVR of the CV- and CV+ groups were compared using the Mann-Whitney U test (GraphPad Prism; GraphPad Software, La Jolla, CA, USA), and presented as medians with interquartile ranges (IQR) as data were non-normally distributed.

Heterogeneity of emphysema was determined using a semi-automated computer-based quantitative analysis of HRCT scans as described previously [9, 10]. Density histogram analysis using a -910 Hounsfield unit threshold defined the emphysema involvement (%) in each lobe. The heterogeneity score was derived by the difference in emphysema scores between lobes.

Clinical Measures

Clinical outcomes were judged in reference to the minimally important clinical difference (MCID). These were defined as an improvement of $\geq 15\%$ in FEV₁ [15], an improvement of ≥ 26 m in the 6MWT [16] and an improvement of ≥ 4 points on the SGRQ [15]. Between-group data were compared using the Mann-Whitney U test (GraphPad Prism).

Results

Baseline Characteristics

Of the 105 patients enrolled, 9 were excluded. All of the 96 patients remaining underwent the EBV procedure (mean number of valves per patient = 3.5; median = 3; range = 1–9). The number of valves used per patient was left to the discretion of the investigator taking into account airway size and patient anatomy with the objective of achieving complete occlusion of the target lobe. Subsequently, 16 of these 96 patients were removed from the final analysis (6 lacked HRCT, 8 were lost to follow-up, and 2 died of unrelated causes; fig. 1). This left a final population of 80 patients. Of these 80 patients, 51 were classified as CV⁻ and 29 as CV⁺ using Chartis. There were no significant differences between the baseline characteristics of the two groups in terms of demographics or lung function (table 1).

Primary Outcome: TLVR

Main Analysis: Comparisons to Baseline and between CV⁺ and CV⁻ Groups

The CV⁻_{all} group had a median TLVR of 752.7 ml (IQR 218.2–1270.1 ml; 55.7%) that was well in excess of the level previously deemed to indicate significant clinical improvement (350 ml). In contrast, the CV⁺_{all} group did not reach this level (TLVR 98.6 ml, IQR 26.8–232.1 ml; 5.7%). There was a significant difference between TLVR of the two groups ($p < 0.0001$). See table 2 and fig. 2a.

Responder Analysis

CV₋responders vs. CV₋non-responders

Of the 51 CV₋ patients, 36 showed a TLVR of ≥ 350 ml, with a median TLVR of 1,061.4 ml (IQR 736.2–1,882.2 ml; 72.1%). In terms of predicting responders to treatment, this translates into a positive predictive value of 71% (table 2; fig. 2b). Of note, of the 36 CV₋responders, 17 (47%) had valves implanted into the lower lobes. Also 14 (39%) had a heterogeneity score of $\leq 15\%$ indicating a low degree of heterogeneity between lobes (table 1).

CV₊responders vs. CV₊non-responders

Of the 29 CV₊ patients, 24 were non-responders (i.e. failed to show significant TLVR), and this was a response predicted by Chartis. This yields a negative predictive value of 83%. See table 2 and fig. 2b.

Clinical Outcomes

Clinical outcome data are presented in table 2.

FEV₁

The CV_{-all} patients showed a mean percentage increase in FEV₁ of 16 ± 22 from baseline values, and 43% achieved the MCID of $\geq 15\%$. In contrast, the CV_{+all} group only showed a percentage increase of 1 ± 15 ($p = 0.0013$). The CV_{-responders} showed a particularly strong percentage increase of 23 ± 24 , with 58% achieving the MCID of $\geq 15\%$.

6MWT

The improvement in 6MWT was greater in the CV_{-all} group (24 m) than the CV_{+all} group (10 m), but statistical significance was not reached ($p > 0.05$). The CV_{-responders} showed a greater response of 31 m, with 53% reaching the MCID of 26 m.

SGRQ

The CV_{-all} group had a mean reduction in SGRQ score of 10 points, compared to a 5 point reduction in the CV_{+all} group. Between-group differences were not statistically significant ($p > 0.05$). However, 68% of the CV_{-all} group reached or

exceeded the 4 point MCID. The CV_{-responders} achieved a mean reduction of 13 points, and 73% reached the MCID.

Safety

Serious adverse events (SAE) were defined as events requiring (or prolonging) hospitalisation, causing a serious deterioration in health, or death. Chartis did not cause any SAE. After EBV treatment of all patients (n = 96), 19 (20%) experienced an SAE. Two patients died; neither of these deaths was determined to be related to the study procedures. One patient died from a ruptured abdominal aortic aneurysm and the other following spinal surgery. Of the study completers (n = 80), 14% experienced at least one SAE (table 3).

Discussion

Chartis showed positive and negative predictive values of 71% and 83%, respectively. This gives an overall rate of accuracy of 75%.

Historically, LVRS has been restricted to the upper lobes as a result of the increased mortality in a subgroup of patients following lower lobe treatment in the NETT study [7]. Data have been lacking regarding the efficacy of EBV placement in lower lobes. In this study, 17/22 (77%) CV₋ patients with EBV placement in a lower lobe showed a TLVR of ≥ 350 ml. Lower lobes should therefore be considered as potential target lobes for EBV treatment.

The inclusion criteria stated that only patients with heterogeneous emphysema could participate in this study. This assessment was made purely by visual read of the HRCT by the investigator. However, some patients were later re-classified by the blinded core laboratory as not having a high degree of heterogeneity (score $\leq 15\%$). Of the 20 CV₋ patients with a low heterogeneity score, 14 (70%) achieved a TLVR of ≥ 350 ml. This lends weight to the argument that TLVR is dependent upon CV rather than heterogeneity.

It should be noted that in the CV_{+non-responder} group, 75% of patients were treated in the right upper lobe (RUL). This is consistent with current knowledge that there are frequently incomplete fissures between the RUL and right middle lobe (RML). Raasch et al. [17] found that in 50 right lung specimens examined, there

were incomplete fissures between the RUL and RML in 44 (88%) of specimens. In the CV_{-non-responders} group, 47% were treated in the RUL. A possible explanation as to why some of these patients who were assessed as CV₋ did not respond may reflect the anatomy of the fissures between RUL and RML. This may represent a specific challenge for assessment of CV. However, this hypothesis requires further research. Furthermore, the high incidence of CV between the RUL and RML raises the question as to whether LVR and improved clinical outcomes in this patient population could be achieved by EBV placement in both the RUL and RML, either simultaneously or sequentially.

Another feature that was seen in a small number of patients was a “low flow” phenomenon. In this situation, the flow trace of Chartis reduced unusually rapidly after two to three breaths. Possible explanations for this are: (1) collapse of the bronchial wall distal to the inflated balloon or (2) the presence of such large collateral channels that, upon balloon inflation, a reverse flow occurs causing air to escape from the target lobe into the adjacent lobe, thus giving a false CV₋ assessment. This should also be the subject of further research.

Five of twenty-nine CV₊ patients did actually respond to EBV treatment. It is interesting to note the baseline characteristics of these patients in comparison to the other groups. These patients tended to be older, but with higher mean BMI and FEV₁ along with lower mean RV. This is suggestive of a less severe disease state. These patients also achieved outstanding clinical results with 80%, 60% and 67% reaching the MCID for FEV₁, 6MWT and SGRO, respectively. Although the number of patients in this group was small, it raises a question as to whether some patients have specific pulmonary characteristics such that they can benefit from EBV therapy even in the presence of CV. One possible theory is that the collateral channels are of a relatively small calibre with high resistance. This, along with a relatively better preserved lung compliance, may result in the resistance to flow through the EBV being lower than that through the collateral channels, therefore resulting in LVR. Another possibility is that only one lobar segment has no CV with the adjacent segments, thus resulting in improved outcome after EBV treatment. Again, further research is required in this area.

No SAEs were attributed to the use of Chartis. SAEs seen following EBV treatment were few, with pneumothorax being the most frequent complication encountered. All six patients experiencing pneumothorax had a significant TLVR, with five of these classed as 'super-responders' (TLVR $\geq 55\%$). Patients experiencing pneumothorax were treated using standard procedures, and recovered in 3–14 days. Rates of pneumothorax were similar in comparison to the European (5/111) and US (9/214) arms of the VENT study [9, 10].

Because this study was designed to validate the Chartis system, there are some limitations to the interpretation of the secondary functional endpoints. By using a 30-day follow-up, patients may not have had sufficient time to increase their fitness level enough to show improvements on the 6MWT. The long-term 6MWT improvements shown by the patients of Venuta et al. [18] following EBV treatment lend weight to this possibility. Additionally, in view of the short follow-up period, this study is not able to demonstrate whether further improvement occurred after 30 days or if the benefit seen at 30 days was sustained. However, Herth et al. [10] demonstrated that in their patients with complete fissures and lobar occlusion, results were sustained at 12 months. Furthermore, Venuta et al. [18] have recently demonstrated sustained benefit to five years, and data from Hopkinson et al. [19] suggested that atelectasis following EBV treatment was associated with a survival benefit. Finally, as there was no enrolment requirement for patients to undergo pulmonary rehabilitation or optimisation of medical treatment, the potential for variability in our sample was increased.

Conclusion

The Chartis Assessment System is a safe method to predict lung volume reduction and has an accuracy of 75%. Lung volume reduction was associated with good clinical responses. This assessment system can be a useful tool to aid clinicians in planning EBV treatment.

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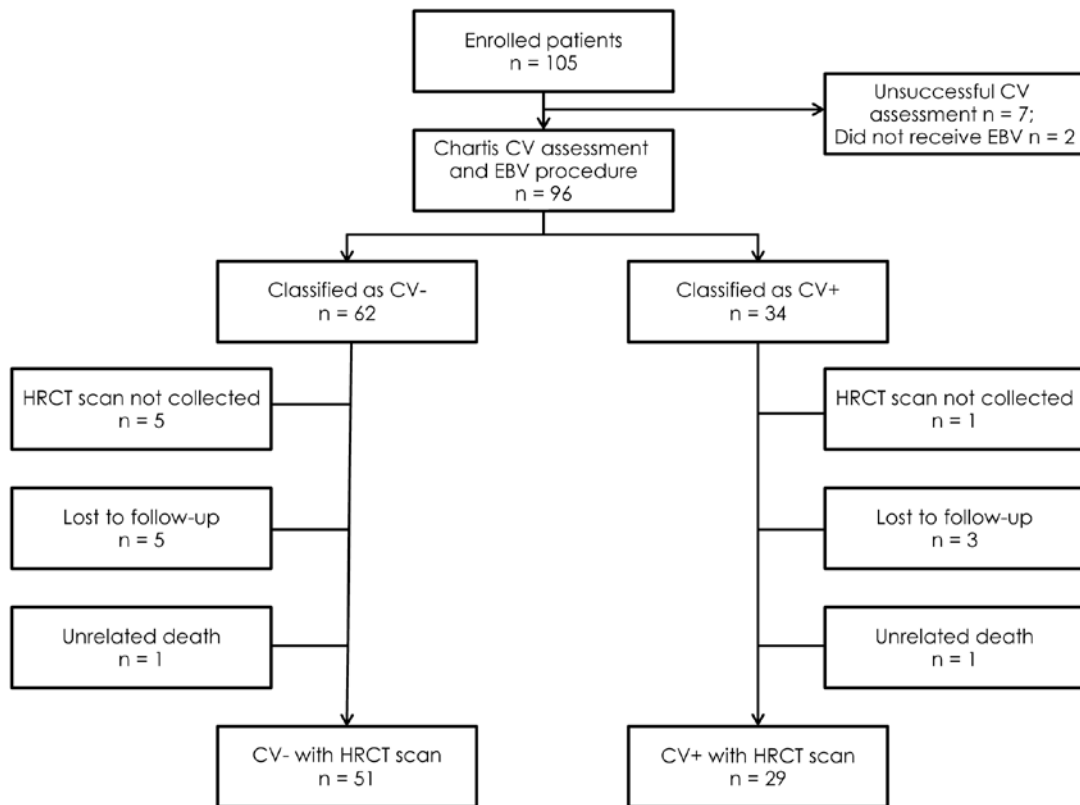


fig. 1

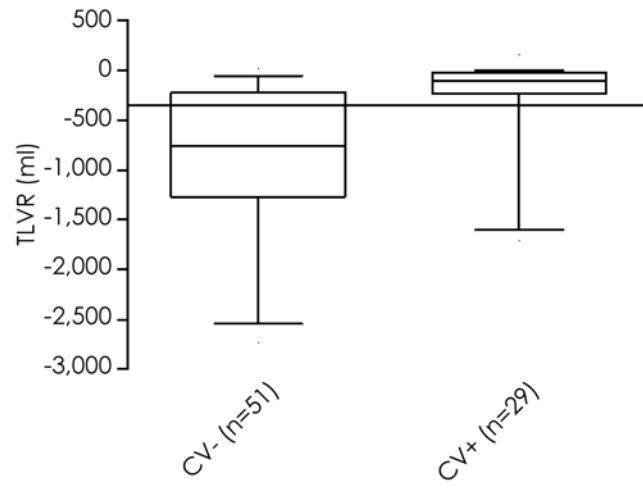


fig. 2a

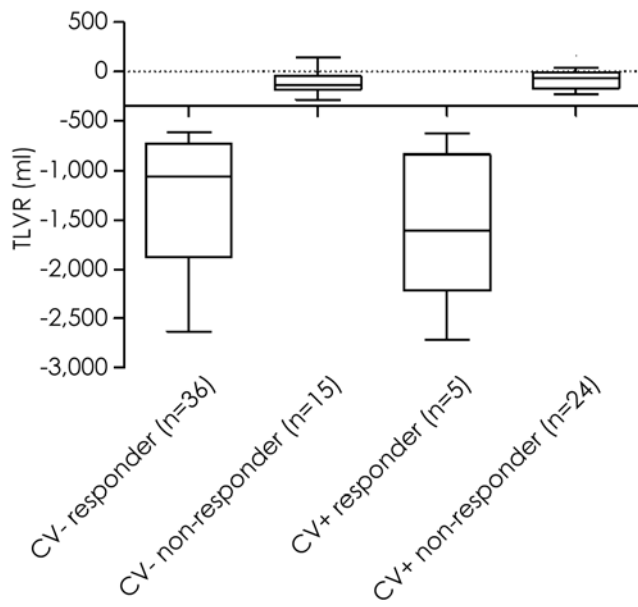


fig. 2b

Table 1. Patient characteristics at baseline

	All patients (n=80)	CV-			CV+		
		all (n=51)	responders (n=36)	non-responders (n=15)	all (n=29)	non-responders (n=24)	responders (n=5)
Demographics							
Age, years	63 ± 9	63 ± 10	63 ± 9	62 ± 10	63 ± 9	62 ± 9	70 ± 5
Male, n	39 (49)	26 (51)	18 (50)	8 (53)	13 (45)	8 (33)	5 (100)
BMI, kg/m ²	24.1 ± 3.3	24.1 ± 3.2	24.3 ± 2.6	23.5 ± 4.4	24.0 ± 3.4	23.4 ± 3.3	26.9 ± 2.5
History of TLVR	7 (7)	5 (9)	3 (8)	2 (13)	2 (7)	0	2 (40)
Smoking status							
Former smoker	77	48	34	14	29	24	5
Current smoker	2	2	2	0	0	0	0
Never smoker	1	1	0	1	0	0	0
Lung function							
% of predicted FEV ₁	32 ± 10	32 ± 10	33 ± 10	31 ± 10	32 ± 10	31 ± 10	38 ± 9
% of predicted D _{LCO}	37 ± 15	37 ± 16	39 ± 17	32 ± 12	37 ± 14	37 ± 15	36 ± 13
% of predicted RV	239 ± 62	237 ± 53	237 ± 50	237 ± 61	242 ± 76	255 ± 76	181 ± 43
% of predicted TLC	134 ± 21	133 ± 18	134 ± 18	131 ± 19	135 ± 25	139 ± 24	119 ± 22
RV/TLC	0.66 ± 0.1	0.66 ± 0.1	0.66 ± 0.09	0.65 ± 0.1	0.67 ± 0.11	0.68 ± 0.11	0.62 ± 0.13
Patient outcomes							
6MWT ^a , m	317 ± 111	327 ± 117	324 ± 108	335 ± 140	298 ± 97	299 ± 102	291 ± 84
SGRQ ^b , points	63 ± 12	63 ± 12	64 ± 12	60 ± 11	63 ± 13	58 ± 16	64 ± 13
Emphysema characteristics							
Alpha-1 antitrypsin deficiency	3 (3)	3 (5)	2 (6)	1 (7)	0	0	0

Heterogeneity							
Heterogeneity score	19 ± 14	20 ± 15	22 ± 15	16 ± 16	18 ± 12	18 ± 14	16 ± 6
≤15% (non-heterogeneous)	36 (44)	20 (39)	14 (39)	6 (40)	16 (55)	12 (50)	4 (80)
Not determined	4 (5)	3 (6)	2 (6)	1 (6)	1 (3)	1 (4)	0
Target lobe							
Right upper	35 (44)	15 (29)	8 (22)	7 (47)	20 (69)	18 (75)	2 (40)
Right middle	2 (3)	2 (4)	1 (3)	1 (7)	0	0	0
Right middle and right lower	1 (1)	1 (2)	0	1 (7)	0	0	0
Right lower	8 (10)	7 (14)	5 (14)	2 (13)	1 (4)	0	1 (20)
Left upper	17 (21)	12 (24)	10 (28)	2 (13)	5 (17)	5 (21)	0
Left lower	17 (21)	14 (27)	12 (33)	2 (13)	3 (10)	1 (4)	2 (40)
History of lung transplant, LVRS or BVR	7 (9)	5 (10)	2 (6)	3 (20)	2 (7)	2 (8)	0
Bullae	5 (6)	3 (6)	2 (6)	1 (7)	2 (7)	1 (4)	1 (20)

Data presented as means ± SD or n (%). BVR = Bronchoscopic volume reduction.

^a All patients (n = 76); CV_{-all} (n = 49); CV_{-responders} (n = 34); CV_{+all} (n = 27); CV_{+non-responders} (n = 3).

^b All patients (n = 58); CV_{-all} (n = 37); CV_{-responders} (n = 26); CV_{-non-responders} (n = 11); CV_{+all} (n = 21); CV_{+non-responders} (n = 18); CV_{+responders} (n = 3).

^c All patients (n = 66); CV_{-all} (n = 41); CV_{-responders} (n = 30); CV_{-non-responders} (n = 11); CV_{+all} (n = 25); CV_{+non-responders} (n = 20); CV_{+responders} (n = 5).

Table 2. Radiological and clinical outcomes

	CV-			CV+		
	all (n=51)	responders (n=36)	non responders (n=15)	all (n=29)	non-responders (n=24)	responders (n=5)
TLVR (median, IQR)						
TLVR, %	55.7 (18.0–92.4)	72.1 (49.8–98.7)	6.4 (2.0–13.5)	5.7 (1.6–16.0)	3.75 (0.3–8.7)	99.2 (40.8–99.6)
TLVR, ml	752.7 (218.2–1,270)	1,061.4 (736.2–1882.2)	132.5 (38.6–187.6)	98.6 (26.8–232.1)	62.2 (3.9–166.2)	1,603.8 (837.1–2216.9)
FEV₁ (mean ± SD)						
Preop., litres	0.87 ± 0.36	0.87 ± 0.35	0.88 ± 0.39	0.82 ± 0.32	0.79 ± 0.33	1.00 ± 0.27
Postop., litres	1.01 ± 0.45	1.07 ± 0.46	0.89 ± 0.40	0.83 ± 0.34	0.75 ± 0.27	1.23 ± 0.36
Absolute Δ	0.14 ± 0.20	0.19 ± 0.21	0.01 ± 0.07	0.01 ± 0.21	-0.04 ± 0.19	0.23 ± 0.12
Percent Δ	16 ± 22	23 ± 24	2 ± 8	1 ± 15	-3 ± 12	23 ± 10
Reached MCID, n (%)	22 (43)	21 (58)	1 (7)	6 (21)	2 (8)	4 (80)
6MWT (mean ± SD)^a						
Preop., m	327 ± 117	324 ± 108	335 ± 140	298 ± 97	299 ± 102	291 ± 84
Postop., m	353 ± 111	358 ± 106	342 ± 125	307 ± 92	304 ± 87	322 ± 120
Difference, m	24 ± 57	31 ± 56	7 ± 56	10 ± 57	5 ± 56	32 ± 65
Reached MCID, n (%)	22 (45)	18(53)	4 (27)	12 (44)	9 (41)	3 (60)
SGRQ (mean ± SD)^b						
Preop., points	63 ± 12	64 ± 12	60 ± 11	63 ± 13	63 ± 13	64 ± 13

Postop., points	51 ± 18	48 ± 19	57 ± 15	58 ± 18	58 ± 16	59 ± 27
Difference, points	-10 ± 13	-13 ± 14	-2 ± 8	-5 ± 15	-4 ± 15	-12 ± 19
Reached MCID, n (%)	25(68)	19 (73)	6 (54)	11 (50)	9 (50)	2 (67)
Other						
Total lung capacity, litres	7.39 ± 1.67	7.24 ± 1.68	7.73 ± 1.65	7.56 ± 1.41	7.76 ± 1.37	6.61 ± 1.33
Residual Volume	4.49±1.22	4.29±1.18	4.97±1.19	4.93±1.53	5.28±1.44	3.25±0.41

MCID defined as an improvement of $\geq 15\%$ in FEV₁, an improvement of ≥ 26 m in the 6MWT and an improvement (i.e. decrease) of ≥ 4 points on the SGRQ. IQR = Interquartile range.

^a CV_{-all} (n = 49); CV_{-responders} (n = 34); CV_{-non-responders} (n = 15); CV_{+all} (n = 27); CV_{+non-responders} (n = 22); CV_{+responders} (n = 5).

^b CV_{-all} (n = 37); CV_{-responders} (n = 26); CV_{-non-responders} (n = 11); CV_{+all} (n = 21); CV_{+non-responders} (n = 18); CV_{+responders} (n = 3).

Table 3. SAE

	All Patients (n=96)	Completed Study (n=80)	CV- (n=51)	CV+ (n=29)
Number having ≥ 1 event	19 (20%)	11 (14%)	6 (12%)	5 (17%)
Type of Events				
Pneumothorax	8	6	4	2
COPD exacerbation	7	4	1	3
Pneumonia	1	1	1	0
Dyspnea	1	1	0	1
Respiratory failure	1	0	0	0

Death	2	0	0	0
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More than 1 SAE per patient is possible