Response to endobronchial valve treatment: it's all about the target lobe

Jorine E. Hartman [1,2], Sharyn A. Roodenburg [1,2], Marlies van Dijk [1,2], T. David Koster [1,2], Karin Klooster[1,2] and Dirk-Jan Slebos [1,2]

[1]Department of Pulmonary diseases, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands. [2]Groningen Research Institute for Asthma and COPD, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands.

Corresponding author: Jorine E. Hartman (j.hartman@umcg.nl)

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Nonresponders to EBV treatment are characterised by a less ideal or non-ideal target lobe, underlining the importance of visually and quantitatively evaluating the potential target lobe for suitability when selecting patients for EBV treatment https://bit.ly/3BVoMKh

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Abstract

Background Bronchoscopic lung volume reduction using endobronchial valves (EBV) has been shown to be beneficial for severe emphysema patients. The most important predictor of treatment response is absence of collateral ventilation between the treatment target and ipsilateral lobe. However, there are still a substantial number of nonresponders and it would be useful to improve the pre-treatment identification of responders. Presumably, predictors of response will be multifactorial, and therefore our aim was to explore whether we can identify response groups using a cluster analysis.

Methods At baseline and 1 year follow-up, pulmonary function, exercise capacity and quality of life were measured. A quantitative chest computed tomography scan analysis was performed at baseline and 2–6 months follow-up. The cluster analysis was performed using a hierarchical agglomerative method.

Results In total, 428 patients (69% female, mean±SD age 61±8 years, forced expiratory volume in 1 s 27±8% predicted, residual volume 254±50% pred) were included in our analysis. Three clusters were generated: one nonresponder cluster and two responder clusters. Despite solid technical procedures, the nonresponder cluster had significantly less clinical response after treatment compared to the other clusters. The nonresponder cluster was characterised by significantly less emphysematous destruction, less air trapping and a higher perfusion of the target lobe, and a more homogeneous distribution of emphysema and perfusion between the target and ipsilateral lobe.

Conclusions We found that target lobe characteristics are the discriminators between responders and nonresponders, which underlines the importance of visual and quantitative assessment of the potential treatment target lobe when selecting patients for EBV treatment.

Introduction

Bronchoscopic lung volume reduction using endobronchial valves (EBV) has been shown to be beneficial for patients with severe emphysema [1]. The most important predictor of treatment response is absence of collateral ventilation between the treatment target and the ipsilateral lobe, which can be verified using the Chartis System [2, 3]. However, despite ruling out the presence of collateral ventilation, the responder rates of four clinical trials that used Chartis ranged between 40% and 87% for different clinical outcomes, indicating room for improvement [1]. The suboptimal response rate could partly be explained by the formation of granulation tissue, which is found in a large number of patients who experience a loss of treatment effect [4]. However, only 13% of all treated patients underwent permanent EBV removal [4]. Besides the absence of collateral ventilation, not much is known in literature about pre-treatment predictors of response to EBV treatment. Most of the cut-off values used for patient selection, as described in expert panel recommendations, are based on inclusion criteria of other lung volume reduction trials and not on

predictor–response analyses [5, 6]. One example of a predictor of response could be the distribution of emphysema, but for example in the STELVIO trial no significant differences were found in clinical outcomes between patients with homogeneous *versus* heterogeneous distributed emphysema [7]. Increasing our knowledge on pre-treatment characteristics associated with treatment response will lead to higher responder rates and potentially prevent patient disappointment afterwards. Presumably, predictors of response will be multifactorial, and therefore our aim was to explore whether we can identify response groups based on pre-treatment characteristics using a cluster analysis.

Methods

Study population

We included patients who were treated with EBV (Zephyr EBV; PulmonX, Redwood City, CA, USA) in our hospital between June 2008 and November 2020. Patients were treated and prospectively followed-up in clinical trials (CHARTIS, STELVIO, IMPACT, TRANSFORM, LIBERATE [2, 7–10]) or after approval of the treatment in regular care and included in the Dutch BREATHE-NL registry (www.clinicaltrials.gov identifier NCT02815683). All patients provided written informed consent.

Measurements

At baseline and 1 year after the EBV treatment the following measurements were performed: post-bronchodilator spirometry, body plethysmography, diffusion capacity, blood gas analysis and a 6-min walk distance (6MWD) test according to the European Respiratory Society/American Thoracic Society guidelines (if applicable) [11–14]. Furthermore, the following questionnaires were completed: modified Medical Research Council scale (mMRC), St George's Respiratory Questionnaire (SGRQ) and the COPD assessment test (CAT) [15–17]. At baseline and after 2–6 months follow-up a chest computed tomography (CT) scan was performed on which a quantitative analysis (QCT) was performed using LungQ software (Thirona, Nijmegen, the Netherlands). The QCT measured variables were lobar volumes (at full inspiration), lobar emphysematous destruction (expressed as the percentage of low attenuation areas (%LAA) <−950 HU at full inspiration), lobar air trapping (%LAA <−856 HU at full expiration), QCT-derived lobar perfusion [18] and standardised airway wall thickness.

Statistical analyses

The self-organising maps (SOM)–Ward method was used for clustering, which is a hierarchical agglomerative cluster method that is based on the Kohonen algorithm [19, 20]. The cluster analysis clusters patients based on their overall similarity on selected variables. The selected variables were sex, age, body mass index, forced expiratory volume in 1 s (FEV_1) (% predicted), residual volume (% pred), inspiratory capacity/total lung volume ratio, diffusing capacity of the lung for carbon monoxide (D_{LCO}) (% predicted), 6MWD, mMRC score, SGRQ total score, CAT total score, partial pressure of arterial oxygen, target volume (at full inspiration), target destruction (%LAA <−950 HU), target air trapping (%LAA <−856 HU on expiration scan), QCT-derived target perfusion, destruction heterogeneity, perfusion heterogeneity, airway wall thickness, relative change in 6MWD between baseline and 1 year follow-up, relative change in SGRQ total score between baseline and 1 year follow-up and relative target volume reduction at 6 weeks follow-up. A paired t-test was performed to investigate changes in clinical outcomes between baseline and the follow-up measurement (data were normally distributed). Differences between identified clusters were tested with an ANOVA with Bonferroni correction or an independent t-test. p-values <0.05 were considered statistically significant. Cluster analysis was performed using Viscovery-SOMine (v7.2; Viscovery Software, Vienna, Austria) and all other statistical analyses were performed using IBM SPSS statistics (version 28; Armonk, NY, USA).

Results

In total, 428 patients were included in the analysis, and patient and procedural characteristics are shown in table 1. 291 (68%) patients visited our hospital for the 1-year follow-up visit (a flowchart of study participants is shown in supplementary figure E1). Significant changes were found between baseline and follow-up for all the clinical outcomes and CT parameters (table 2).

The cluster analysis generated three clusters (figure 1 and supplementary figure E2). Cluster C showed a significantly worse response to treatment in clinical outcomes compared to the other two clusters (clusters A and B) and could therefore be defined as the nonresponder cluster (figure 2, table 3 and supplementary tables E3 and E4).

The most remarkable pre-treatment difference between the two responder clusters and the nonresponder cluster were found in the target lobe characteristics. The nonresponder cluster had significantly less destruction, less air trapping and higher perfusion in the target lobe compared to the responder clusters.

TABLE 1 Patient baseline demographics and procedure characteristics

Patients	428
Female	293 (69)
Age, years	61.3±8.2
Smoking, pack-years	38 (25–48)
FEV_1, % pred	26.5±7.7
RV, % pred	253.7±49.9
D_{LCO}, % pred	38.2±11.8
6MWD, m	327±97
SGRQ, total score	57.5±12.6
Emphysema score, $\%LAA_{-950}$	38.5±7.5
Procedure	
Target lobe	
Left upper lobe	95 (22)
Left lower lobe	147 (34)
Right upper lobe	71 (17)
Right lower lobe	74 (17)
Right middle lobe	11 (3)
Right middle+upper lobe	30 (7)
Valves implanted, n	4.3±1.8
Procedure time, min	14 (9–19)
Hospital admission, days	5 (4–7)

Data are presented as n, n (%), mean±SD or median (interquartile range). FEV_1: forced expiratory volume in 1 s; RV: residual volume (% predicted according to the Global Lung Initiative reference values); D_{LCO}: diffusing capacity of the lung for carbon monoxide; 6MWD: 6-min walk distance; SGRQ: St George's Respiratory Questionnaire; $\%LAA_{-950}$: percentage of low attenuation areas <−950 HU on the inspiratory computed tomography scan.

Furthermore, the heterogeneity in destruction and perfusion between target and ipsilateral lobes was significantly less ($p<0.001$).

When looking at the two responder clusters, these can be best distinguished from each other based on disease state. Cluster A has less advanced disease based on pulmonary function, exercise capacity and quality of life compared to cluster B. Despite the difference in baseline characteristics, both clusters showed significant and comparable improvements in clinical outcomes after EBV treatment.

Regarding target lobe volume reduction (TLVR), only cluster A (the responder cluster with less advanced disease) had a significant higher TLVR compared to the other two clusters (table 2). The TLVR in all clusters was well above the established minimal important difference of −22.4% [21]. Furthermore, the number of TLVR responders did not differ between clusters (supplementary table E3).

Discussion

We found that despite a technically optimal procedure, nonresponders to EBV treatment are characterised by a less ideal or non-ideal target lobe: less emphysematous destruction, a more homogeneous distribution

TABLE 2 Changes in clinical outcomes and lobe volumes after endobronchial valve treatment

	1 year follow-up	2–6 months follow-up	Patients (valid)	p-value
Δ FEV_1, L	0.16±0.18		290	<0.001
Δ RV, L	−0.69±0.64		274	<0.001
Δ 6MWD, m	44.8±69.3		263	<0.001
Δ SGRQ, total score	−11.0±15.8		291	<0.001
Δ CAT, total score	3.0±6.0		219	<0.001
Δ Target lobe volume reduction, mL		1360±700	371	<0.001

Data are presented as mean±SD or n, unless otherwise stated. Difference between baseline and 1 year or 2–6 months follow-up were tested using a paired t-test (data were normally distributed). Δ: change between baseline and follow-up; FEV_1: forced expiratory volume in 1 s; RV: residual volume; 6MWD: 6-min walk distance; SGRQ: St George's Respiratory Questionnaire, CAT: COPD assessment test.

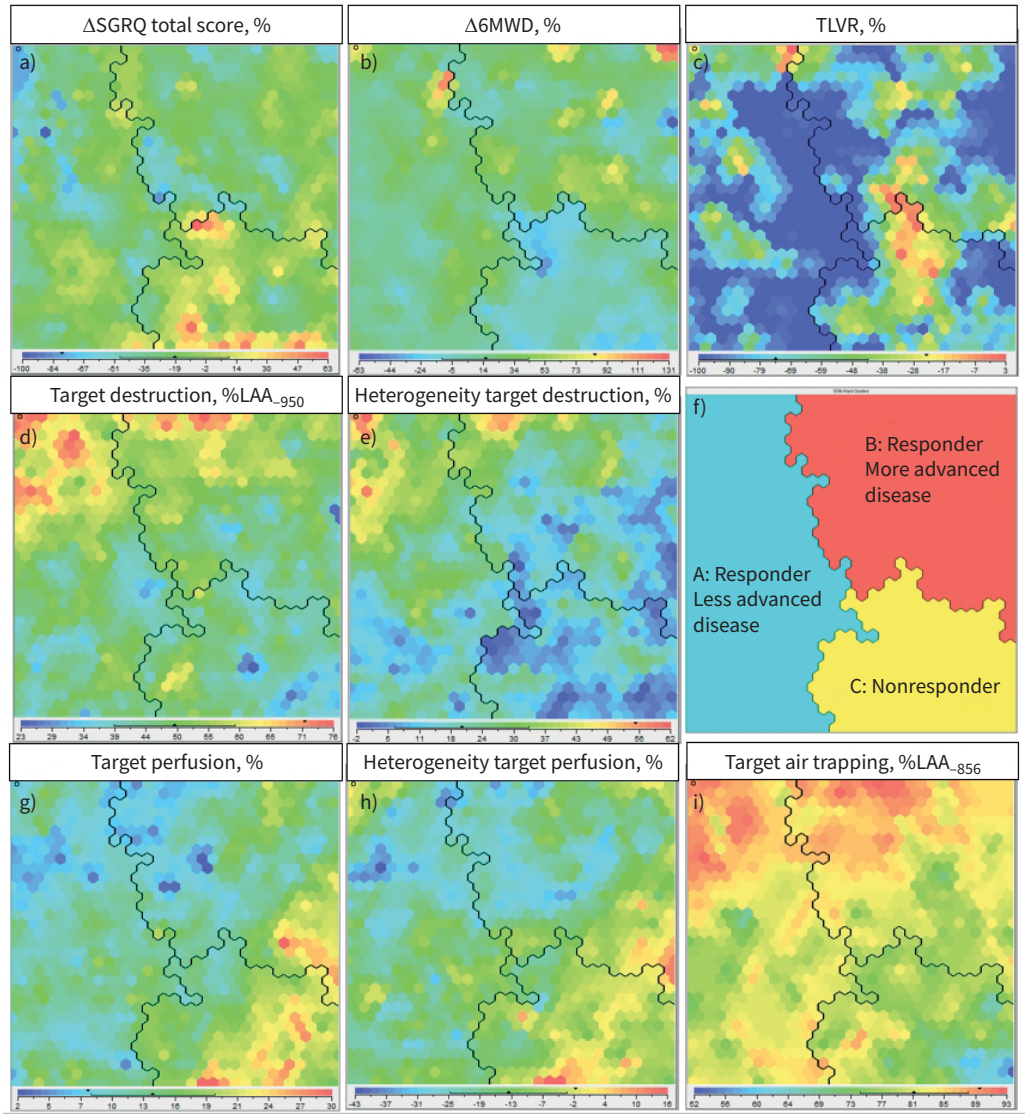

FIGURE 1 Graphical presentation of the cluster analysis created with panels from Viscovery software. f) The cluster analysis created three clusters, based on the multidimensional response profile of the patients. The more the characteristics of the subjects are alike, the closer they are on the map, and consequently the more they differ the further away they are from each other. The colours represent the size of the attribute. Red indicates the highest value or response and blue the lowest value or response. a) Change (Δ) in St George's Respiratory Questionnaire (SGRQ) total score between 1 year follow-up and baseline (relative); b) change in 6-min walk distance (6MWD) between 1 year follow-up and baseline (relative); c) target lobe volume reduction (TVLR) at 2–6 months follow-up (relative); d) target destruction (percentage of low attenuation areas <–950 HU on the inspiratory computed tomography scan ($\%LAA_{-950}$); destruction heterogeneity; g) target perfusion; h) perfusion heterogeneity; and i) target air trapping ($\%LAA_{-856}$). Panels of all attributes included in the cluster analysis can be found in supplementary figure E2.

of both emphysema destruction and perfusion, less air trapping and more preserved perfusion. Baseline disease severity characteristics, such as the amount of hyperinflation or level of exercise capacity, were not indicators of response.

Our results indicate that evaluation of the potential target lobe(s) for emphysematous destruction, perfusion and air trapping is key when selecting patients for EBV treatment. This target lobe assessment can be done visually and by QCT, which is already needed to evaluate the intactness of the fissure, the main predictor of treatment success. Previously, we showed that the interobserver agreement between expert CT assessors

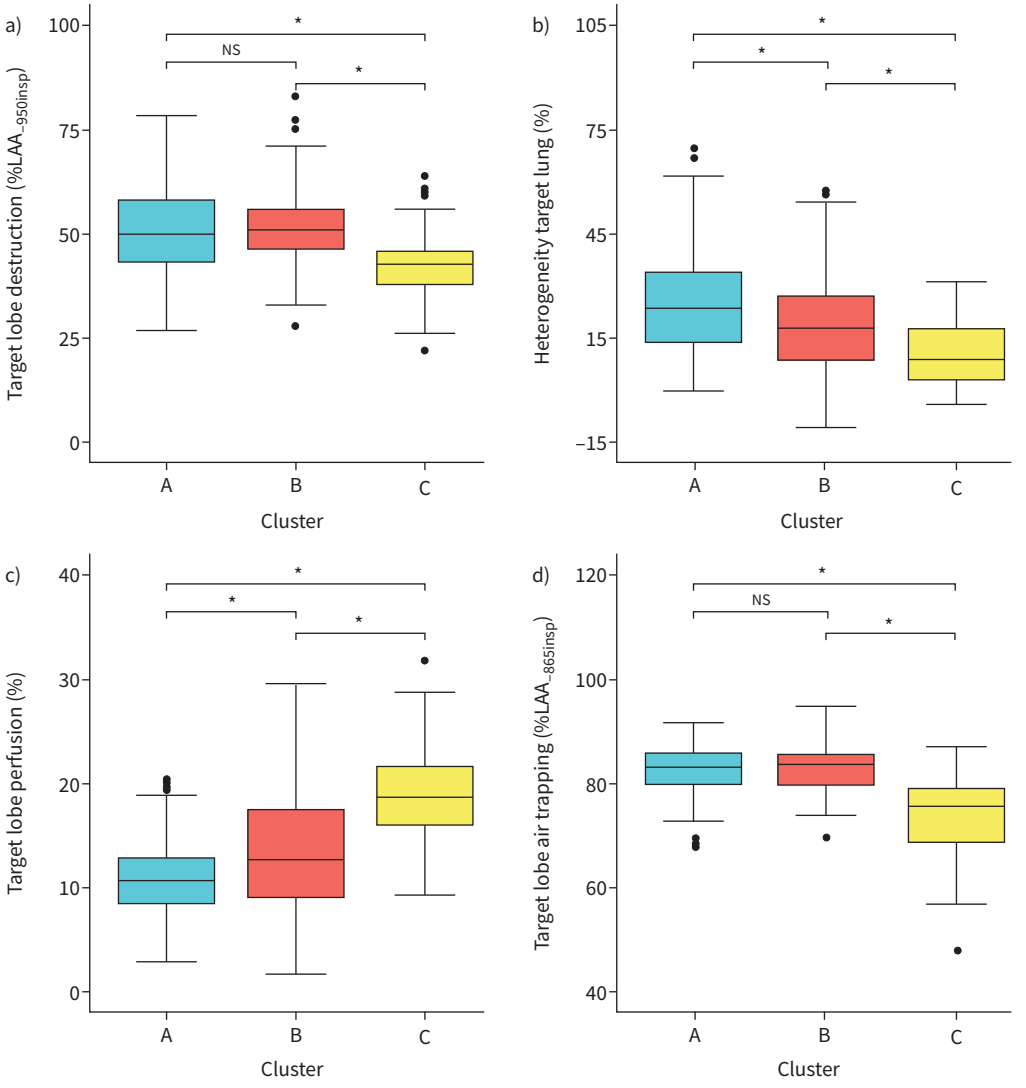

FIGURE 2 Boxplots showing the differences in computed tomography (CT) characteristics between the three clusters. Differences between clusters were tested with an ANOVA with Bonferroni correction. Cluster A: responder group with less advanced disease; cluster B: responder group with more advanced disease; cluster C: nonresponder group; $\%LAA_{-950insp}$: percentage of low attenuation areas <–950 HU on the inspiratory CT scan; $\%LAA_{-856exp}$: percentage of low attenuation areas <–856 HU on the expiratory CT scan; NS: nonsignificant. *: p<0.05.

in determining the most destructed lobe was only fair to moderate [22]. The agreement improved when including the information from the QCT analysis. Therefore, it would be recommended to evaluate the target lobe with multiple assessors, for example, in a multidisciplinary team meeting, and make use of QCT analysis.

In addition, our results showed that baseline disease severity characteristics, such as residual volume, FEV_1, 6MWD and SGRQ were not indicators of response. This is consistent with previous publications that showed that patients with baseline measures below (previously) recommended selection criteria (such as residual volume ⩽175% pred [23] or FEV_1 ⩽20% pred [24, 25]) can also significantly benefit from EBV treatment [5]. Furthermore, EBV treatment was found to be safe and clinically beneficial in patients with a lower level of D_{LCO} (⩽20% pred [26, 27]) or clinically relevant hypercapnia (partial pressure of carbon dioxide ⩾45 mmHg [28, 29]). Of course, it would be helpful, especially for pulmonary physicians starting up a lung volume reduction programme at their hospital to have guidance on patient selection and thus clear cut-off values on standard baseline measures such as pulmonary function outcomes. However,

TABLE 3 Differences in clinical outcomes and baseline characteristics between clusters

	A: Responder, less advanced disease	B: Responder, more advanced disease	C: Nonresponder	p-value
Patients	181 (42)	149 (35)	98 (23)	
Change in clinical outcome				
ΔSGRQ total score, %	−26.8±25.9^{C}	−24.6±24.3^{C}	1.5±30.2^{A,B}	**<0.001**
Δ6MWD, %	17.8±18.5^{B,C}	27.2±34.4^{A,C}	−2.5±21.8^{A,B}	**<0.001**
TLVR, %	−82.2±27.6^{B,C}	−70.7±30.0^{A}	−64.0±33.8^{A}	**<0.001**
ΔRV, %	−17.2±10.8^{C}	−14.1±13.9^{C}	−8.3±10.6^{A,B}	**<0.001**
ΔFEV_1, %	24.5±23.6^{C}	23.9±26.6^{C}	10.9±16.9^{A,B}	**<0.001**
Baseline characteristics				
Female	116 (64.1)	109 (73.2)	68 (69.4)	0.206
Age, years	61.54±9.12	60.55±7.78	62.18±6.67	0.277
BMI, $kg \cdot m^{-2}$	24.55±3.6^{B}	23.04±3.80^{A}	23.97±3.30	**<0.001**
mMRC score	2.48±0.61^{B}	3.13±0.61^{A,C}	2.55±0.58^{B}	**<0.001**
FEV_1, % pred	31.44±7.84^{B,C}	21.14±4.68^{A,C}	25.63±4.64^{A,B}	**<0.001**
RV, % pred	230.5±40.5^{B}	289.4±49.8^{A,C}	243.0±32.8^{B}	**<0.001**
IC/TLC, %	25.85±5.14^{B,C}	17.42±3.90^{A,C}	22.4±3.90^{A,B}	**<0.001**
D_{LCO}, % pred	44.17±12.17^{B,C}	29.69±7.70^{A,C}	36.52±7.89^{A,B}	**<0.001**
P_{aO_2}, kPa	9.49±1.18^{B}	8.67±1.24^{A,C}	9.30±1.09^{A,B}	**<0.001**
6MWD, m	369.7±81.9^{B}	253.3±81.4^{A,C}	354.8±79.9^{B}	**<0.001**
SGRQ total score, units	54.49±11.75^{B}	63.66±11.72^{A,C}	54.35±12.23^{B}	**<0.001**
Baseline CT characteristics				
Target volume inspiratory, mL	1945±696	1881±648	1803±433	0.198
Heterogeneity target perfusion, %	−18.11±9.11^{B,C}	−14.35±11.95^{A,C}	−5.79±8.47^{A,B}	**<0.001**
Pi_{10}, mm	2.64±0.33	2.71±0.27^{C}	2.59±0.29^{B}	**<0.001**

Data are presented as n (%) or mean±SD, unless otherwise stated. Differences between groups were tested with ANOVA with Bonferroni correction. Bold type represents statistical significance. Δ: change between baseline and follow-up (2–6 months after baseline for target lobar volume reduction (TLVR); 1 year after treatment for the other variables); SGRQ: St George's Respiratory Questionnaire; 6MWD: 6-min walk distance; RV: residual volume; FEV_1: forced expiratory volume in 1 s; BMI: body mass index; mMRC: modified Medical Research Council scale; IC: inspiratory capacity; TLC: total lung capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; P_{aO_2}: partial pressure of arterial oxygen; CT: computed tomography; Pi_{10}: standardised airway wall thickness; ^{ABC}: statistically significant differences between clusters are indicated with the corresponding superscript.

our results, together with these previous publications suggest that using strict selection criteria might lead to undertreatment of potential responders and that it is more important to look at the bigger picture in which the "quality" of the target lobe plays a critical role. Another example highlighting the importance of the quality of the target lobe is a recently published study that investigated EBV treatment exclusively in the middle lobe [30]. This study showed that treating only the middle lobe, which is often the smallest lobe, can also lead to significant clinical benefit for the patient, but the authors also stated that this was only the case when the middle lobe was the clear target showing the most pronounced destruction.

It would be useful to have some guidance on how to evaluate the quality of the target lobe. As mentioned before, stringent selection criteria are not desirable. However, it would be useful to further investigate which CT characteristics are most important or to investigate whether desired ranges of a combination of multiple CT characteristics can be found. It would be very interesting to investigate this, but a larger dataset would be needed.

A remarkable finding was that the two responder clusters could be separated by the severity of COPD, as cluster B had clearly more advanced disease compared to cluster A. Notably, this difference in COPD severity did not impact the response to treatment, as both clusters had significant and clinically relevant improvements in FEV_1, residual volume, 6MWD and SGRQ. Furthermore, the nonresponder cluster had less advanced disease in terms of lung function, exercise capacity and quality of life compared to cluster B. This finding emphasises that baseline severity disease characteristics are of less importance for patient selection than target lobe characteristics.

With regard to borderline eligible cases it can be a difficult decision whether or not to treat these patients. Fortunately, the EBV treatment is reversible in case there is no treatment response. However, the treatment is associated with complications such as a pneumothorax [31] and comes with significant costs [32–34]. Furthermore, patients can become disappointed when the treatment does not work out as they expected. It

would be useful to be able to inform the patients pre-treatment when they have a less optimal treatment profile, and with that, lower their expectations. Therefore, we propose to review all cases, but especially the borderline eligible and less straightforward cases, in a multidisciplinary review board which should include at least a radiologist and an experienced interventional bronchoscopist to evaluate the CT scan for potential target lobe(s) [35, 36].

There are other factors that could influence the response to EBV treatment that we did not include in our analysis. One of these factors could be comorbidities, as it is known that comorbidities are highly prevalent in COPD patients [37, 38]. It would have been interesting to include comorbidities in our analyses, but unfortunately we did not have complete information on them. However, an earlier study demonstrated, in a small population, that established pulmonary hypertension did not affect the efficacy or safety of EBV treatment [39]. Moreover, recent research has shown that EBV treatment even can improve cardiac pre-load, myocardial contractility and cardiac output, suggesting even a potential positive influence on comorbidities [40].

One limitation of our paper is that the patients included in our analysis were already selected for treatment based on known selection criteria and the decision of the treating physicians. Consequently, a selection bias could have occurred. However, the patients were included over a 12-year period during which treatment and knowledge about patient selection has improved. Moreover, despite the potential selection bias, the analysis still included a substantial number of nonresponders.

To conclude, our results showed that nonresponse to EBV treatment is associated with a less than ideal or nonoptimal target lobe, based on emphysema, perfusion and air trapping. This underscores the importance of visually and quantitatively evaluating the potential target lobe's suitability when selecting patients for EBV treatment.

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Data sharing statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions: J.E. Hartman, S.A. Roodenburg and D-J. Slebos designed the analysis, wrote the first draft of the manuscript and made revisions after feedback from co-authors. All the authors meet the definition of an author as stated by the International Committee of Medical Journal Editors, and all have seen and approved the final manuscript.

Conflict of interest: D-J. Slebos reports grants or contracts from PulmonX Corp., PneumRx/BTG/Boston Scientific, FreeFLowMedical, Nuvaira, PulmAir, GALA, CSA Medical and Apreo, outside the submitted work; consulting fees from PulmonX Corp., PneumRx/BTG/Boston Scientific, Nuvaira and Apreo, outside the submitted work; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from PulmonX Corp., PneumRx/BTG/Boston Scientific and Nuvaira, outside the submitted work; support for attending meetings and/or travel from PulmonX Corp., PneumRx/BTG/Boston Scientific and Nuvaira, outside the submitted work; and his institution is in receipt of study material/devises from PulmonX Corp., PneumRx/BTG/Boston Scientific, FreeFLowMedical, Nuvaira, PulmAir, GALA and CSA Medical, outside the submitted work. The remaining authors have nothing to disclose.

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