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Original research article

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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], 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

J.E. Hartman, PhD

Department of Pulmonary diseases AA11

University Medical Centre Groningen

PO Box 30001, 9700 RB Groningen

The Netherlands

Tel : +31 503612357, E-mail: j.hartman@umcg.nl

Take home message: Non-responders to EBV treatment were characterized by a less or non-ideal target lobe. Our results underline the importance to visually and quantitatively evaluate the potential target lobe for suitability when selecting patients for EBV treatment.

ABSTRACT

BACKGROUND Bronchoscopic lung volume reduction using endobronchial valves (EBV) has 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 non-responders 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 clusteranalysis.

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

RESULTS In total 428 patients (69%female, age 61±8 years, FEV_1 27±8%pred, RV 254±50%pred) were included in our analysis. Three clusters were generated: 1 non-responder and 2 responder clusters. Despite solid technical procedures, the non-responder cluster had significantly less clinical response after treatment compared to the other clusters. The non-responder 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 non-responders which underlines the importance of visual and quantitative assessment of the potential treatment target lobe when selecting patients for EBV treatment.

Keywords: Emphysema, bronchoscopic intervention, lung volume reduction

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 with 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 to87% for different clinical outcomes, indicating room for improvement[4]. 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[5]. However, only 13% of all treated patients underwent permanent EBV removal[5]. 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 actual predictor-response analyses[6, 7]. 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[8]. 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's (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, 8–11]) or after approval of the treatment in regular care and included in the Dutch BREATHE-NL registry (NCT02815683). All patients provided written informed consent.

Measurements

At baseline and one year after the EBV treatment the following measurements were performed: post-bronchodilator spirometry, bodyplethysmography, diffusion capacity, blood gas analysis and a 6-minute walk distance (6MWD) test according to the European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines (if applicable)[12–15]. Furthermore, the following questionnaires were filled out: modified Medical Research Council scale (mMRC), St. George's Respiratory Questionnaire (SGRQ) and the COPD assessment test (CAT)[16–18]. At baseline and after two to six 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 consisted of: lobar volumes (at full inspiration), lobar emphysematous destruction (expressed as the percentage of low attenuation areas (%LAA) below <-950 Hounsfield units (HU) at full inspiration), lobar air trapping (%LAA< -856 HU at full expiration), QCT-derived lobar perfusion[19] and airway wall thickness (Pi10)."

Statistical analyses

The Self-Organizing Maps(SOM)-Ward method was used for clustering, which is a hierarchical agglomerative cluster method that is based on the Kohonen algorithm[20, 21]. The cluster analysis clusters patients based on their overall similarity on selected variables. The selected variables were: sex, age, body mass index (BMI), forced expiratory volume in 1 second (FEV_1) (%predicted), residual volume (RV) (%predicted), inspiratory capacity/ total lung volume (IC/TLC) ratio, diffusing capacity for carbon monoxide (DLCO) (%predicted), 6MWD, mMRC score, SGRQ total score, CAT total score, partial pressure of arterial oxygen (PaO_2), target volume (at full inspiration), target destruction (percentage of low attenuation areas (%LAA) below <-950 Hounsfield units (HU)), target air trapping (%LAA< -856 HU on expiration scan), QCT derived target perfusion, destruction heterogeneity, perfusion heterogeneity, airway wall thickness (Pi10), relative change in 6MWD between baseline and one year follow up, relative change in SGRQ total score between baseline and one year follow up and relative target volume reduction at six weeks follow up. A paired t-test was performed to investigate changes in clinical outcomes between baseline and the follow up measurement (data was normally distributed). Differences between identified clusters were tested with an ANOVA with Bonferroni correction or an independent t-test. P-values below 0.05 were considered statistically significant. Cluster analysis was performed using Viscovery-SOMine v7.2 (Viscovery-Software-GmbH, 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. Two hundred and ninety-one patients (68%) visited our hospital for the one year follow up visit (flowchart of study participants is shown in the online supplement, Figure E1). Significant changes were found between baseline and follow up for all the clinical outcomes and CT parameters (see table 2).

The cluster analysis generated three clusters (see Figure 1 and Figure E2 in online supplement). Cluster C showed a significantly worse response to treatment in clinical outcomes compared to the other two clusters (cluster A and B) and could therefore be defined as the non-responder cluster (see Figure 2, Table 3 and Table E3 and table E4 in the online supplement).

The most remarkable pre-treatment difference between the two responder and the non-responder clusters were found in the target lobe characteristics. The non-responder cluster had significant less destruction, less air trapping and higher perfusion in the target lobe compared to the responder clusters. Furthermore, the heterogeneity in destruction and perfusion between target and ipsilateral lobe 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. But 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%[22]. Furthermore, the number of TLVR responders did not differ between clusters (Table E3 in online supplement).

DISCUSSION

We found that despite a technical optimal procedure, non-responders to EBV treatment are characterized by a less or non-ideal target lobe: less emphysematous destruction, a more homogeneous distribution 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 in determining the most destructed lobe was only fair to moderate[23]. 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.

Our results also showed that baseline disease severity characteristics, such as RV, FEV_1, 6MWD and SGRQ, were not indicators of response. This is consistent with a couple of previous publications that already showed that patients with baseline measures below (previously) recommended selection criteria such as RV≤175% of predicted)[24] or FEV_1 ≤20% of predicted[25, 26], can also significantly benefit from EBV treatment[6]. Furthermore, EBV treatment was found to be safe and clinically beneficial, inpatients with a lower level of DLCO (≤20% of predicted)[27, 28] or clinical relevant hypercapnia (pCO2≥ 45mm Hg).[29, 30] 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, 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 paper that investigated EBV treatment exclusively in the middle lobe[31]. This paper 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, RV, 6MWD and SGRQ. Furthermore, the non-responder cluster had less advanced disease in terms of lung function, exercise capacity and quality of life compared to cluster B. This findings once again 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 endobronchial valve treatment is a reversable treatment in case there is no treatment response. However, the treatment is associated with complications such as a pneumothorax[32] and comes with significant costs[33–35]. Furthermore, patients can become disappointed when the treatment did not work out as they expected. It would therefore 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. We therefore propose to review all cases, but especially the borderline eligible and less straight-forward 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)[36, 37].

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[38, 39]. 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[40]. Moreover, recent research has shown that EBV treatment even can improve cardiac preload, myocardial contractility and cardiac output, suggesting even a potential positive influence on comorbidities[41].

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 the treatment and knowledge about patient selection has improved. Moreover, despite the potential selection bias, the analysis still included a substantial amount of non-responders.

To conclude, our results showed that non-response to EBV treatment is associated with a less-than ideal or non-optimal 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.

Authors contributions

JEH, SAR and DJS 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.

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TABLES and Figure legends

Table 1: Patient baseline demographics and procedure characteristics (n=428)

Gender, *female*	293 (69%)
Age, *years*	61.3 ± 8.2
Packyears, *years*	38 (25-48)
FEV_1, *%predicted*	26.5 ± 7.7
RV, *%predicted*	253.7 ± 49.9
DLCO, *%predicted*	38.2 ± 11.8
6MWD, *meter*	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, *number*	4.3 ± 1.8
Procedure time, *minutes*	14 (9-19)
Hospital admission, *days*	5 (4-7)

Data are presented as n(%), mean ± standard deviation or median (interquartile range).
FEV_1: forced Expiratory volume in 1 second, RV: residual volume (%predicted according to the GLI reference values), DLCO: diffusing capacity for carbon monoxide, 6MWD: 6 minute walk distance, SGRQ: St. George's Respiratory Questionnaire, $\%LAA_{-950}$: percentage of low attenuation areas below -950 Hounsfield units on the inspiratory computed tomography scan.

Table 2: Changes in clinical outcomes and lobe volumes after endobronchial valve treatment.

	1 year FU	**n (valid)**	**p-value**
Δ FEV_1, *liter*	0.16 ± 0.18	290	<0.001
Δ RV, *liter*	-0.69 ± 0.64	274	<0.001
Δ 6MWD, *meter*	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
	2 to 6 months FU	**n (valid)**	**p-value**
Δ Target lobe volume reduction, *mL*	1360 ± 700	371	<0.001

Data are presented as mean ± standard deviation, number or p-value.
Difference between baseline and 1 year or 2 to 6 months follow up were tested with a paired t-test (data were normally distributed). Δ= change between baseline and follow up. FEV_1: Forced expiratory volume in 1 second, RV: residual volume, 6WMD: 6-minute walk distance, SGRQ: St. George's respiratory questionnaire, CAT: COPD assessment test.

Table 3: Differences in clinical outcomes and baseline characteristics between clusters

Cluster *Description*	**A** **Responder** Less advanced disease	**B** **Responder** more advanced disease	**C** **Non-responder**	**p-value**
Number	181 (42%)	149 (35%)	98 (23%)	
Change in clinical outcome				
Δ SGRQ_totalscore, *%*	-26.8 ± 25.9^{C}	-24.6 ± 24.3^{C}	1.5 ± 30.2^{A,B}	**<0.001**
Δ 6MWD, *%*	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**
Δ RV, *%*	-17.2 ± 10.8^{C}	-14.1 ± 13.9^{C}	-8.3 ± 10.6^{A,B}	**<0.001**
Δ FEV_1, *%*	24.5 ± 23.6^{C}	23.9 ± 26.6^{C}	10.9 ± 16.9^{A,B}	**<0.001**
Baseline characteristics				
Gender, *female*	116 (64.1%)	109 (73.2%)	68 (69.4%)	0.206
Age, *year*	61.54 ± 9.12	60.55 ± 7.78	62.18 ± 6.67	0.277
BMI, *kg/m²*	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, *%predicted*	31.44 ± 7.84^{B,C}	21.14 ± 4.68^{A,C}	25.63 ± 4.64^{A,B}	**<0.001**
RV, *%predicted*	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**
DLCO, *%predicted*	44.17 ± 12.17^{B,C}	29.69 ± 7.70^{A,C}	36.52 ± 7.89^{A,B}	**<0.001**
PO_2, *kPa*	9.49 ± 1.18^{B}	8.67 ± 1.24^{A,C}	9.30 ± 1.09^{A,B}	**<0.001**
6MWD, *meter*	369.7 ± 81.9^{B}	253.3 ± 81.4^{A,C}	354.8 ± 79.9^{B}	**<0.001**
SGRQ totalscore, *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**
Pi10, *mm*	2.64 ± 0.33	2.71 ± 0.27^{C}	2.59 ± 0.29^{B}	**<0.001**

Data are presented as number (percentage) or mean ± standard deviation. Difference between groups were tested with ANOVA with Bonferroni correction. ^{ABC}: Statistically significant differences between clusters are indicated with the corresponding superscript. Δ= change between baseline and follow up (TLVR between 2 to 6 months after baseline for the other variables 1 year after treatment). SGRQ: St. George's Respiratory questionnaire, 6MWD: 6-minute walk distance, TLVR: target lobar volume reduction, RV: residual volume, FEV_1: Forced expiratory volume in 1 second, BMI: body mass index, mMRC: modified Medical Research council scale, IC: inspiratory capacity, TLC: total lung capacity, DLCO: diffusing capacity for carbon monoxide, PO_2: partial pressure of oxygen, CT: computed tomography.

Figure 1: Graphical presentation of the cluster analysis (selection of panels)

Legend: Figure created with panels from Viscovery software. The clusteranalysis created 3 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. A red colour indicates the highest value or response and the blue colour the lowest value or response. Attributes included in the figure are: Change in SGRQ total score between 1 year follow up(relative), change in 6MWD between 1 year follow up and baseline (relative), target lobe volume reduction at 2 to 6 months follow up (relative), target destruction ($\%LAA_{-950}$), destruction heterogeneity, target perfusion, perfusion heterogeneity and target air trapping ($\%LAA_{-856}$). Panels of all attributes included in the cluster analysis can be found in the Online Supplement Figure S2.

Figure 2: Boxplots showing the differences in CT characteristics between the 3 clusters

Legend: Figure shows the differences between clusters in computed tomography (CT) characteristics. Differences between clusters were tested with an ANOVA with Bonferroni correction. *** p-value below 0.05, NS: not significant. Cluster A: Responder group with less advanced disease, Cluster B: Responder group with more advanced disease, Cluster C: Non-responder group. $\%LAA_{-950insp}$: percentage of low attenuation areas below -950 Hounsfield units on the inspiratory CT scan, $\%LAA_{-856exp}$: percentage of low attenuation areas below -856 Hounsfield units on the expiratory CT scan.

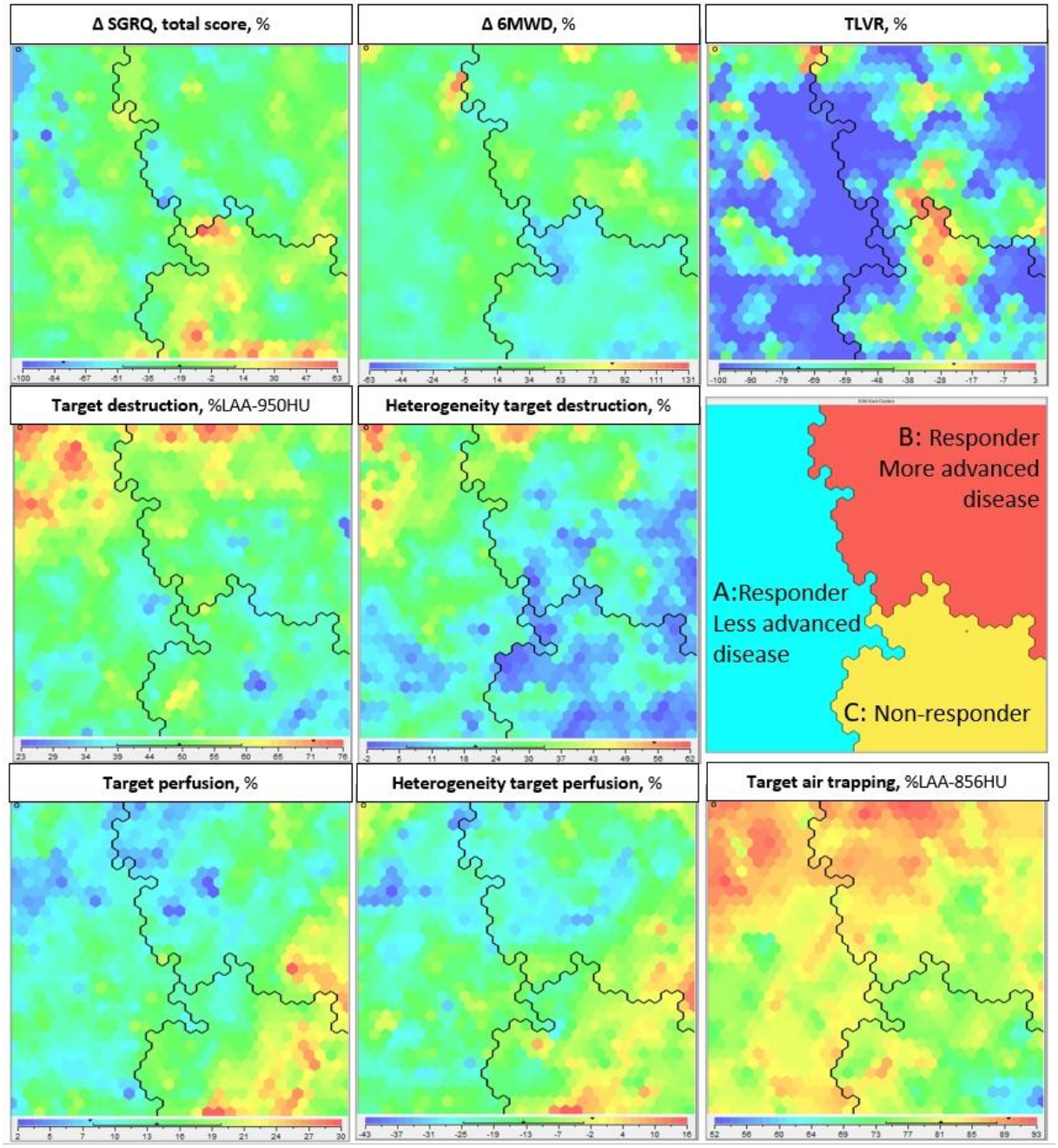


Figure 1: Graphical presentation of the cluster analysis (selection of panels) Legend: Figure created with panels from Viscovery software. The clusteranalysis created 3 clusters, based on the multidimensional response profile of the patients. The more the characteristics of the subjects are alike the 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. A red colour indicates the highest value or response and the blue colour the lowest value or response. Attributes included in the figure are: Change in SGRQ total score between 1 year follow up(relative), change in 6MWD between 1 year follow up and baseline (relative), target lobe volume reduction at 2 to 6 months follow up (relative), target destruction (%LAA-950), destruction heterogeneity, target perfusion, perfusion heterogeneity and target air trapping (%LAA-856). Panels of all attributes included in the cluster analysis can be found in the Online Supplement Figure S2.

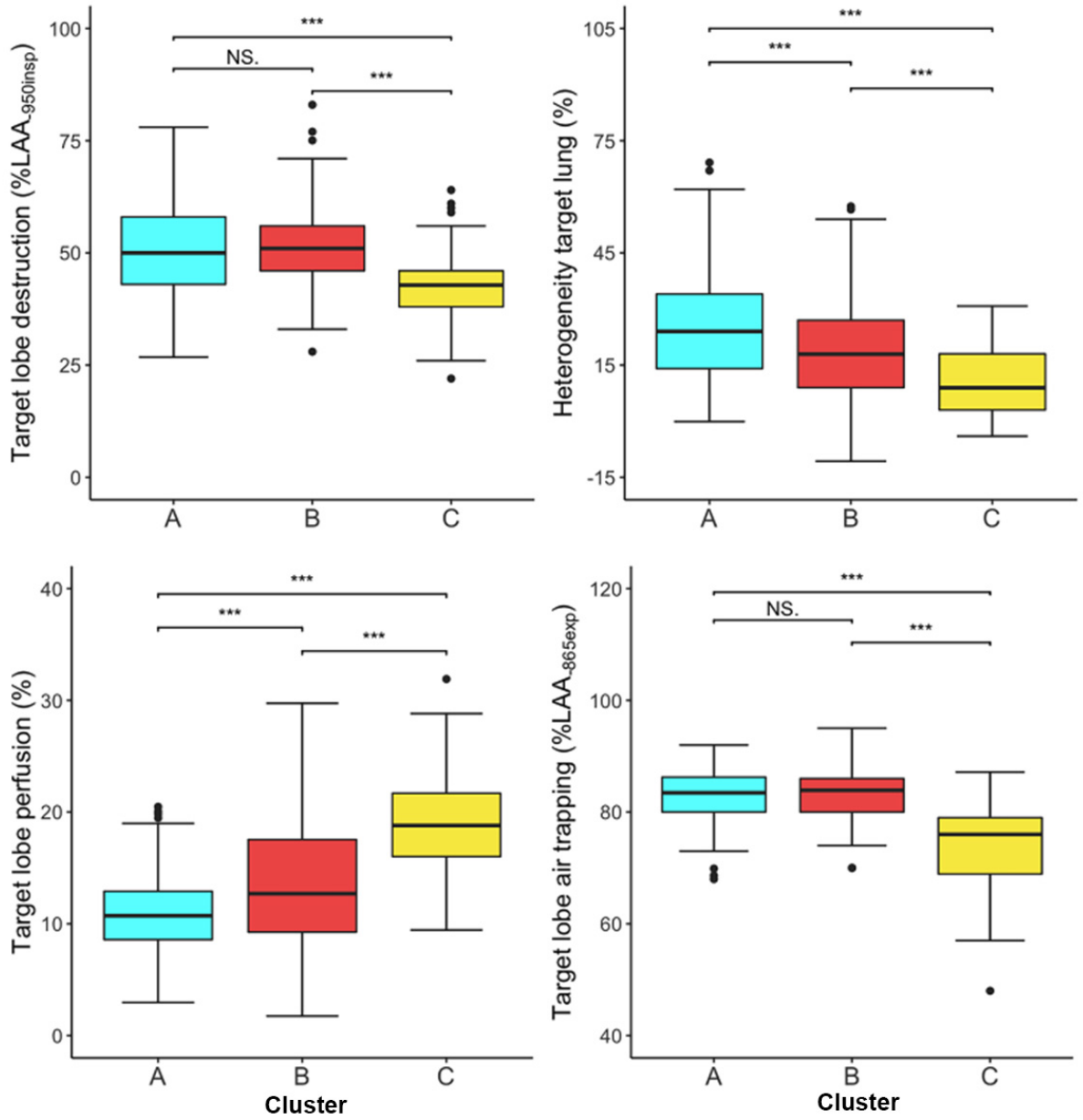


Figure 2: Boxplots showing the differences in CT characteristics between the 3 clusters Legend: Figure shows the differences between clusters in computed tomography (CT) characteristics. Differences between clusters were tested with an ANOVA with Bonferroni correction. *** p-value below 0.05, NS: not significant. Cluster A: Responder group with less advanced disease, Cluster B: Responder group with more advanced disease, Cluster C: Non-responder group. %LAA-950insp: percentage of low attenuation areas below -950 Hounsfield units on the inspiratory CT scan, %LAA-856exp: percentage of low attenuation areas below -856 Hounsfield units on the expiratory CT scan.

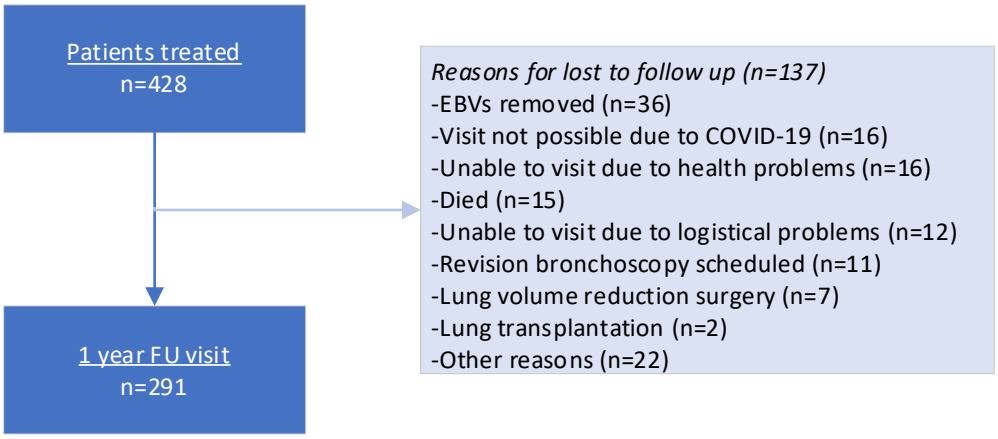
ONLINE DATA SUPPLEMENT

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], Dirk-Jan Slebos[1,2]

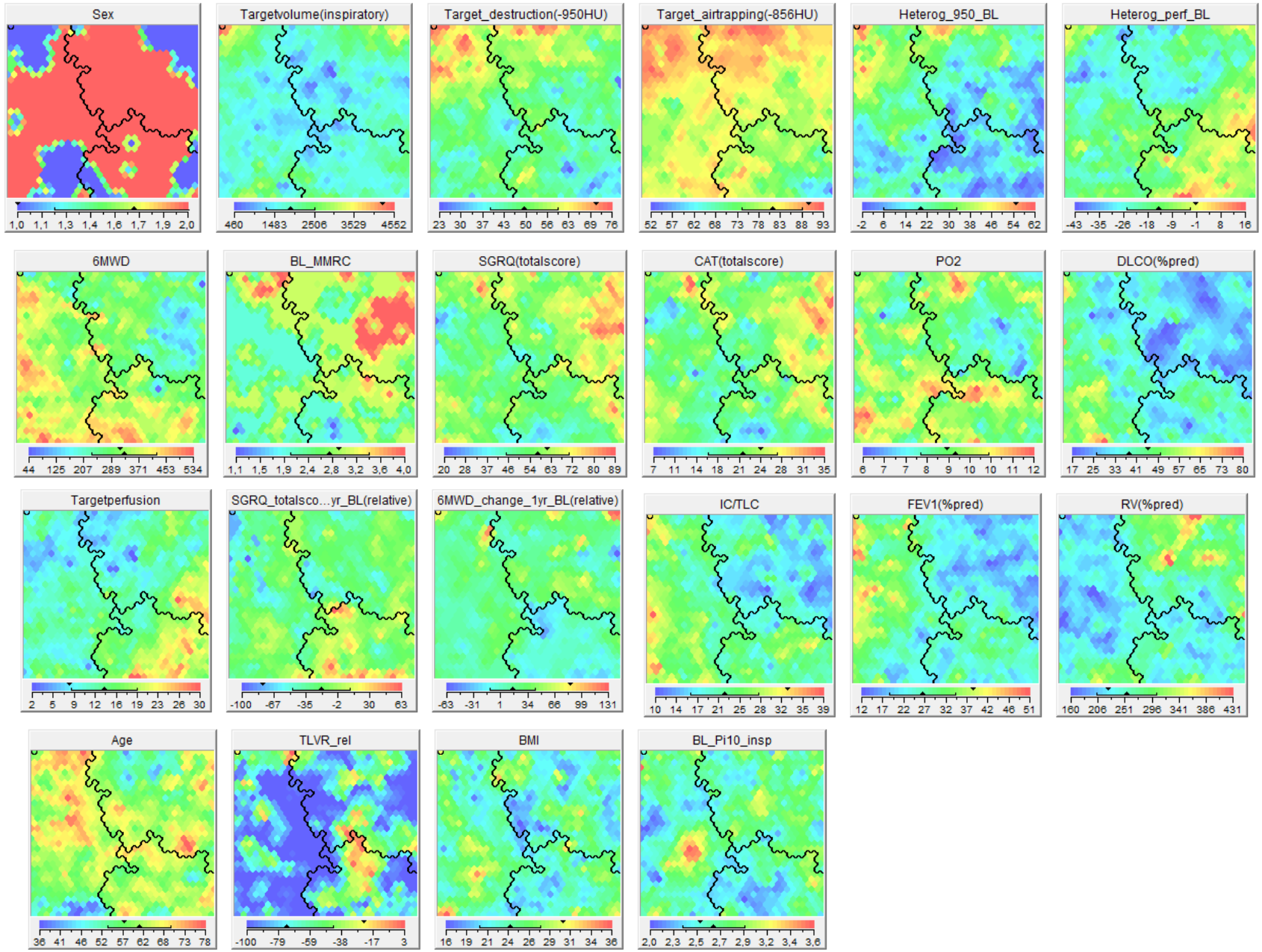
Content:

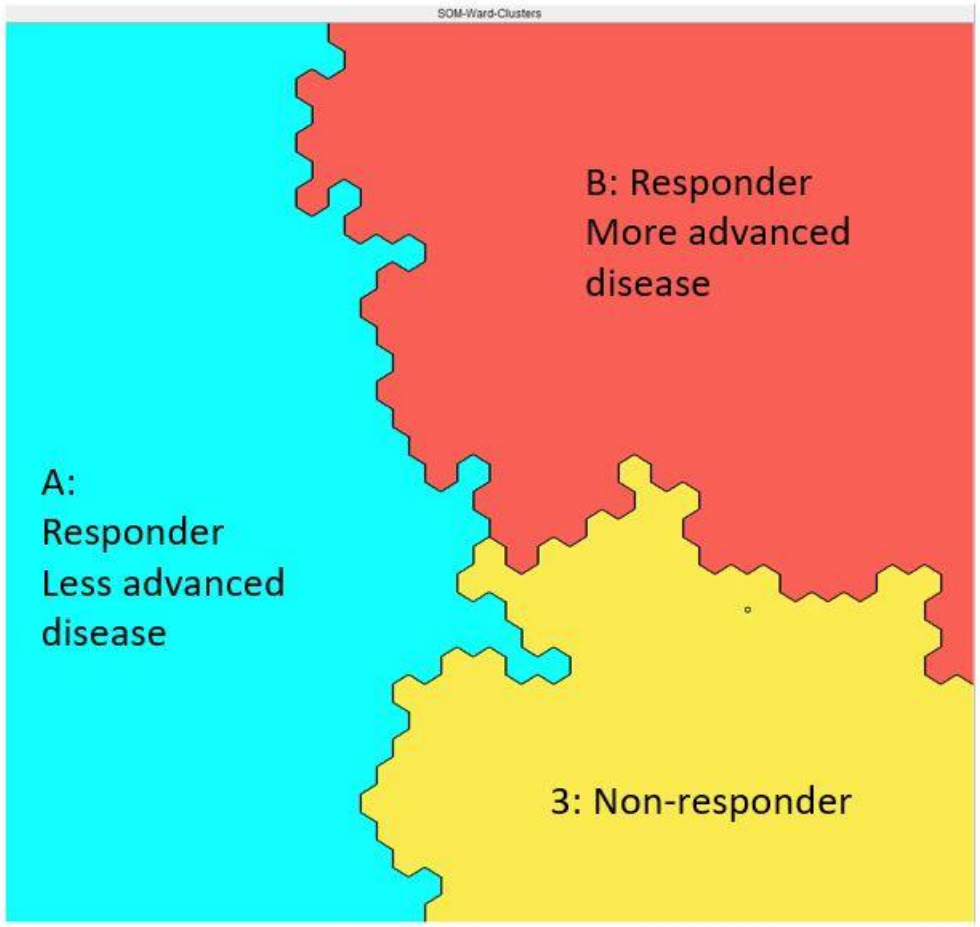
Figure E1. Flowchart of study participants



Legend: EBVs: endobronchial valves, FU: follow up.

Figure E2: Graphical presentation of the cluster analysis (complete)





Legend: Figure created with panels from Viscovery software. The clusteranalysis created 3 clusters, based on the multidimensional response profile of the patients. The more subjects are similar the closer they are on the map and the more they differ the further away they are from each other. The colours represent the size of the attribute. A red colour indicates the highest value or response and the blue colour the lowest value or response. All selected variables for the cluster analysis are shown: Sex, age, BMI, FEV_1 (%predicted), RV (%predicted), IC/TLC ratio, DLCO (%predicted), 6MWD, mMRC score, SGRQ total score, CAT total score, pO_2, Target volume (inspiratory), target destruction ($\%LAA_{-950}$), target air trapping ($\%LAA_{-856}$), target perfusion, destruction heterogeneity, perfusion heterogeneity, Pi10, change in 6MWD between 1 year follow up and baseline (relative), change in SGRQ total score between 1 year follow up and baseline and target volume reduction at 2 to 6 months follow up (relative).

Table E3: Differences in clinical outcomes and baseline characteristics between clusters (Complete table)

Cluster *Description*	**A** **Responder** Less advanced disease	**B** **Responder** more advanced disease	**C** **Non-responder**	**p-value**
Number	181 (42%)	149 (35%)	98 (23%)	
Change in clinical outcome				
Δ SGRQ_totalscore, *%*	-26.8 ± 25.9[C]	-24.6 ± 24.3[C]	1.5 ± 30.2[A,B]	**<0.001**
Δ 6MWD, *%*	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**
TLVR responders¶, *%*	94.4	94.2	90.0	**0.365***
Δ RV, *%*	-17.15 ± 10.8[C]	-14.08 ± 13.9[C]	-8.32 ± 10.6[A,B]	**<0.001**
Δ FEV_1, *%*	24.5 ± 23.6[C]	23.9 ± 26.6[C]	10.9 ± 16.9[A,B]	**<0.001**
Baseline characteristics				
Gender, *female*	116 (64.1%)	109 (73.2%)	68 (69.4%)	0.206
Age, *year*	61.54 ± 9.12	60.55 ± 7.78	62.18 ± 6.67	0.277
BMI, kg/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, *%predicted*	31.44 ± 7.84[B,C]	21.14 ± 4.68[A,C]	25.63 ± 4.64[A,B]	**<0.001**
RV, *%predicted*	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]	22.40 ± 3.90[A,B]	**<0.001**
DLCO, *%predicted*	44.17 ± 12.17[B,C]	29.69 ± 7.70[A,C]	36.52 ± 7.89[A,B]	**<0.001**
PO_2, *kPa*	9.49 ± 1.18[B]	8.67 ± 1.24[A,C]	9.30 ± 1.09[A,B]	**<0.001**
6MWD, *meter*	369.7 ± 81.9[B]	253.3 ± 81.4[A,C]	354.8 ± 79.9[B]	**<0.001**
SGRQ totalscore, *units*	54.49 ± 11.75[B]	63.66 ± 11.72[A,C]	54.35 ± 12.23[B]	**<0.001**
CAT totalscore, *units*	20.81 ± 5.46[B]	23.41 ± 5.43[A,C]	19.99 ± 5.18[B]	**<0.001**
Baseline CT characteristics				
Target volume inspiratory, *mL*	1945 ± 696	1881 ± 648	1803 ± 433	0.198
Target destruction, $\%LAA_{-950}$	51.28 ± 10.75[C]	51.36 ± 9.09[C]	42.34 ± 7.50[A,B]	**<0.001**
Heterogeneity target destruction, *%difference*	25.28 ± 13.62[B,C]	19.49 ± 13.03[A,C]	10.68 ± 8.78[A,B]	**<0.001**
Target perfusion, *%*	10.97 ± 3.49[B,C]	13.72 ± 5.73[A,C]	18.94 ± 4.44[A,B]	**<0.001**
Heterogeneity target perfusion, *%*	-18.11 ± 9.11[B,C]	-14.35 ± 11.95[A,C]	-5.79 ± 8.47[A,B]	**<0.001**
Target air trapping, $\%LAA_{-856}$	82.98 ± 5.14[C]	83.09 ± 4.93[C]	73.99 ± 7.60[A,B]	**<0.001**
Pi10, *mm*	2.64 ± 0.33	2.71 ± 0.27[C]	2.591 ± 0.286[B]	**<0.001**

Data are presented as number (percentage) or mean ± standard deviation. Difference between groups were tested with ANOVA with Bonferroni correction or *Chi-square test. [ABC]:Statistically significant differences between clusters are indicated with the corresponding superscript. Δ= change between baseline and follow up. SGRQ: St. George's Respiratory questionnaire, 6MWD: 6-minute walk distance, TLRV: target lobar volume reduction, RV: residual volume, FEV_1: Forced expiratory volume in 1 second, BMI: body mass index, mMRC: modified Medical Research council scale, IC: inspiratory capacity, TLC: total lung capacity, DLCO: diffusing capacity for carbon monoxide, PO_2: partial pressure of oxygen, CAT: COPD assessment test, CT: computed tomography, $\%LAA_{-950}$: percentage of low attenuation areas below -950 Hounsfield

units on the inspiratory CT scan, $\%LAA_{-856}$: percentage of low attenuation areas below -856 Hounsfield units on the expiratory CT scan.¶: Responders defined as a change in TLVR above the established minimal important difference of -22.4%(21).

Table E4: Differences in clinical outcomes and baseline characteristics between the combined responder clusters and the non-responder cluster

Cluster	**A+B**	**C**	
Description	*Responder*	*Non-responder*	**p-value**
Number	330 (77%)	98 (23%)	
Change in clinical outcome			
Δ SGRQ_totalscore, %	-26.0 ± 25.2	1.5 ± 30.2	**<0.001**
Δ 6MWD, %	21.5 ± 26.2	-2.5 ± 21.8	**<0.001**
TLVR, %	-77.3 ± 29.2	-64.0 ± 33.8	**<0.001**
Δ RV, *%*	-16.0 ± 12.1	-8.3 ± 10.6	**<0.001**
Δ FEV_1, *%*	24.3 ± 24.8	10.9 ± 16.9	**<0.001**
Baseline characteristics			
Sex, male (%)	105 (31.8%)	30 (30.6%)	0.902
Age, year	61.11 ± 8.5	62.18 ± 6.67	0.185
BMI, kg/m^2	23.9 ± 3.8	24.0 ± 3.30	0.800
mMRC score	2.76 ± 0.69	2.55 ± 0.58	**0.007**
FEV_1, %predicted	26.8 ± 8.4	25.6 ± 4.6	0.080
RV, %predicted	256.9 ± 53.6	243.0 ± 32.8	**0.002**
IC/TLC, %	22.1 ± 6.2	22.4 ± 3.9	0.543
DLCO, %predicted	38.7 ± 12.8	36.5 ± 7.9	0.061
PO_2, kPa	9.1 ± 1.3	9.3 ± 1.1	0.189
6MWD, meter	318.0 ± 100.0	354.8 ± 79.9	**<0.001**
SGRQ totalscore, units	58.5 ± 12.6	54.4 ± 12.2	**0.005**
CAT totalscore	22.1 ± 5.6	20.0 ± 5.2	**0.004**
Baseline CT characteristics			
Target volume inspiratory, mL	1916 ± 674	1803 ± 433	0.052
Target destruction, *%LAA-950*	51.3 ± 10.0	42.3 ± 7.5	**<0.001**
Heterogeneity target destruction, %	22.7 ± 13.6	10.7 ± 8.8	**<0.001**
Target perfusion, %	12.2 ± 4.8	18.9 ± 4.4	**<0.001**
Heterogeneity target perfusion, %	-16.4 ± 10.6	-5.8 ± 8.5	**<0.001**
Target air trapping, *%LAA-856*	83.0 ± 5.0	74.0 ± 7.6	**<0.001**
Pi10, mm	2.67 ± 0.30	2.59 ± 0.29	**0.025**

Data are presented as number (percentage) or mean ± standard deviation. Difference between groups were tested with an independent t-test. Δ= change between baseline and follow up. SGRQ: St. George's Respiratory questionnaire, 6MWD: 6-minute walk distance, TLRV: target lobar volume reduction, RV: residual volume, FEV_1: Forced expiratory volume in 1 second, BMI: body mass index, mMRC: modified Medical Research council scale, IC: inspiratory capacity, TLC: total lung capacity, DLCO: diffusing capacity for carbon monoxide, pO_2: partial pressure of oxygen, CAT: COPD assessment test, CT: computed tomography, $\%LAA_{-950}$: percentage of low attenuation areas below -950 Hounsfield units on the inspiratory CT scan, $\%LAA_{-856}$: percentage of low attenuation areas below -856 Hounsfield units on the expiratory CT scan.