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Published in:
ERJ Open Research

DOI:
10.1183/23120541.00279-2023

Publication date:
2023

The impact of emphysema heterogeneity on treatment response after endobronchial valve treatment

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Shareable abstract (@ERSpublications)
Heterogeneity index, the difference in emphysematous destruction between the targeted and ipsilateral lobe, cannot distinguish responders from nonresponders for endobronchial valve treatment, but does affect the degree of clinical improvement https://bit.ly/3pnpkpx

Cite this article as: Roodenburg SA, Klooster K, Slebos D-J, *et al*. The impact of emphysema heterogeneity on treatment response after endobronchial valve treatment. *ERJ Open Res* 2023; 9: 00279-2023 [DOI: 10.1183/23120541.00279-2023].

Received: 1 May 2023
Accepted: 20 June 2023

Abstract

Background Lung volume reduction with endobronchial valves can significantly improve functional outcomes in patients with advanced emphysema. The extent and spatial distribution pattern of emphysema shows considerable heterogeneity, which might affect response to endobronchial valve treatment. Our aim was to study the effect of emphysema heterogeneity on change in clinical outcomes after endobronchial valve treatment.

Methods Data were collected from our national registry of patients who received endobronchial valve treatment between 2016 and 2020. We assessed the association between the heterogeneity index, absolute difference in destruction between the target and ipsilateral lobe, and relative change in forced expiratory volume in 1 s (FEV_1), residual volume (RV), St George's Respiratory Questionnaire (SGRQ) and 6-min walk distance (6MWD) at 6-week, 6-month and 12-month follow-up.

Results In total, 236 patients were included. Heterogeneity index was significantly associated with improvements in FEV_1, RV and 6MWD at all follow-up visits, and in SGRQ at the 6- and 12-month follow-up visits. The majority of patients, independent of heterogeneity index, showed clinically meaningful improvements based on minimal important difference thresholds.

Conclusions Heterogeneity index influences the degree of clinical improvement after endobronchial valve treatment where in general a more heterogeneous distribution translates to larger improvements. However, patients with a more homogeneous distribution also showed clinically meaningful improvements. Therefore, we believe emphysema heterogeneity alone should not be used as a decisive patient selection criterion, but should be weighed in the context of all other relevant patient and target lobe characteristics when deciding on a patient's treatment eligibility.

Introduction

Emphysema is one of the main phenotypes of COPD [1]. It is pathologically characterised by permanent enlargement of air spaces distal to the terminal bronchioles with destruction of the alveolar walls [2]. Computed tomography (CT) is a sensitive method to diagnose emphysema by the detection of low-attenuation areas (LAA). The extent and spatial distribution pattern of emphysema throughout the lungs shows considerable heterogeneity and there is some evidence to suggest that this influences the response to lung volume reduction treatments [3–9].

The National Emphysema Treatment Trial (NETT) was the first large prospective lung volume reduction trial which compared lung volume reduction surgery (LVRS) to standard of care [5, 6]. In this study, a visual CT scoring system was used to quantify the amount and distribution of emphysema throughout the lungs. Patients with heterogeneous upper lobe predominant emphysema were found to have the best treatment

response. Furthermore, patients with a homogeneous emphysema distribution in combination with a very low forced expiratory volume in 1 s (FEV_1) were found to have an increased risk of death [5, 6].

Bronchoscopic lung volume reduction with endobronchial valves (EBVs) was developed as a minimally invasive alternative to LVRS. Adopted from the NETT findings, heterogeneous emphysema was a selection criterion in all, except for one, of the EBV trials [7–12]. In the first trials, the distribution of emphysema on CT images was scored visually [7–9, 12]. Currently, it is known that this visual scoring method has a substantial interobserver variability [13] and *post hoc* quantitative CT (QCT) analysis has shown that patients with varying degrees of heterogeneity were included in these first trials [7–9]. Currently, no clear definition is available to distinguish heterogeneous and homogeneous emphysema, but a 15% difference in destruction between the targeted and ipsilateral nontargeted lobes is most frequently used [4, 7, 9, 11]. Using this cut-off, it has been shown that both patients with homogeneous and heterogeneous emphysema significantly benefit from EBV treatment compared to standard of care, but that the treatment effect is less pronounced in patients with homogeneous emphysema [4, 9].

Overall, in clinical trials the number of patients with a low degree of emphysema heterogeneity between the treatment target and the ipsilateral nontargeted lobe treated with EBVs is low. Consequently, the current knowledge on the actual effect of emphysema heterogeneity on response to EBV treatment is limited. The aim of the current study was to assess the effect of emphysema heterogeneity on change in clinical outcomes after EBV treatment in a "regular care" treatment population.

Methods

Study population and data collection

The present study used data from the BREATHE-NL (Bronchoscopic Emphysema Treatment in the Netherlands) registry, a Dutch prospective database with the objective to record the "regular care" effects of bronchoscopic lung volume reduction treatments (ClinicalTrials.gov identifier NCT02815683). Due to the noninvasive nature of this registry, formal ethics approval was waived by the medical ethics committee of the University Medical Centre Groningen (UMCG). Nevertheless, all patients provided informed consent. Data are captured before treatment (baseline) and at 6 weeks, 6 months, 12 months and annually thereafter up to 5 years after treatment. Collected measures include demographics, post-bronchodilator pulmonary function testing, 6-min walk distance (6MWD) except at 6-weeks follow-up, and health-related quality of life measured using the St George's Respiratory Questionnaire (SGRQ). A thin-slice chest CT scan is acquired pre-treatment at full inspiration and full expiration, and 6 weeks post-treatment at full inspiration.

From the BREATHE-NL registry, we collected baseline, 6-week, 6-month and 12-month follow-up data from patients who received EBV treatment between September 2016 and December 2020 in the UMCG. Patients were excluded from further analyses when there was 1) no quantitative CT analysis at baseline, 2) EBVs were only implanted in the right middle lobe or 3) when none of the follow-up visits in the first year after treatment were attended.

Quantitative CT analyses

All CT images were analysed using LungQ software (Thirona, Nijmegen, the Netherlands). Each lung lobe was automatically segmented with manual edits by a professional technologist if necessary. Destruction was defined as the percentage of LAA with values <−950 HU at full inspiration ($\%LAA_{-950insp}$) and air trapping as the percentage of LAA with values <−856 HU on the expiratory CT scan ($LAA_{-856exp}$). A CT-derived lobar perfusion was determined using an AI-based method which has shown a high correlation to single photon-emission computed tomography-derived perfusion [14].

Heterogeneity index

Currently, there is no gold standard to define interlobar emphysema heterogeneity, and multiple approaches are available [15]. We calculated the heterogeneity index as the difference in destruction ($\%LAA_{-950insp}$) between the treatment target lobe and the ipsilateral nontargeted lobe, including the right middle lobe. If the targeted lobe was one of the lobes of the right lung, or if it included the right middle lobe, a combined destruction score was calculated by summing the destruction of the two lobes weighted by their volume (supplementary figure E1 includes a calculation example). Previous EBV trials frequently used a LAA threshold of −910 HU to define destruction. We compared our heterogeneity index with the heterogeneity index that would have been calculated if we used the LAA −910 HU threshold, and found a very strong association (ρ=0.944) (supplementary figure E2).

Statistics

Spearman's correlation coefficient (ρ) was used to assess the strength of the association between the heterogeneity index and relative change in clinical outcomes 6 weeks, 6 months and 12 months post-EBV treatment, and between heterogeneity index and radiological changes on the CT scan 6 weeks post-treatment.

The previously reported heterogeneity threshold to define emphysema distribution was used to categorise patients in two subgroups: homogeneous (heterogeneity index <15%) and heterogeneous (heterogeneity index ⩾15%) [4, 7–11]. The following minimal important differences (MIDs) were used to categorise patients as responders (reached the MID threshold) or nonresponders: change (Δ) in FEV_1 ⩾10%, Δ residual volume (RV) ⩽−8.6% [16], ΔSGRQ ⩽−11.1% [17], Δ6MWD ⩾10% [18] and Δ target lobe volume ⩽−22.4% [19]. For all subgroup analyses, between-group comparisons were performed using independent t-test, Mann–Whitney U-test or Chi-squared test where appropriate. Paired t-test or Wilcoxon signed-rank test were used to perform within-group comparisons.

The ability of the heterogeneity index to predict responders on FEV_1, RV, SGRQ and 6MWD, 6 months following EBV treatment was assessed using receiver operator characteristic (ROC) curves and their corresponding area under the curve (AUC).

All statistical analyses were performed using the R project version 4.2.1 (R Core Team 2022, Vienna, Austria). p-values <0.05 were considered statistically significant.

Results

Patient characteristics

Within the study period, 253 patients received EBV treatment, of whom 236 were considered eligible for inclusion in our analysis (figure 1). The 6-week, 6-month and 12-month follow-up visits were attended by 220, 197 and 177 patients, respectively (reasons for nonattendance are shown in supplementary table E1).

Table 1 shows the baseline characteristics of the study population. Using the 15% heterogeneity cut-off value, 141 (60%) patients were allocated to the heterogeneous and 95 (40%) patients to the homogeneous subgroup. Airflow obstruction was more severe in the group of patients with homogeneous emphysema. Furthermore, all quantitative CT-derived measures were significantly different between these subgroups. The target lobe in the homogeneous subgroup showed a significant lower volume, less destruction, less air trapping and a higher perfusion compared to the heterogeneous subgroup.

Association between the heterogeneity index and change in clinical outcomes

Heterogeneity index was significantly associated with an improvement in FEV_1, RV and 6MWD at all included time points, and with improvements in SGRQ total score at the 6- and 12-month follow-up visits, but not at 6-weeks follow-up visit (table 2, figure 2 and supplementary figure E3). For all treatment

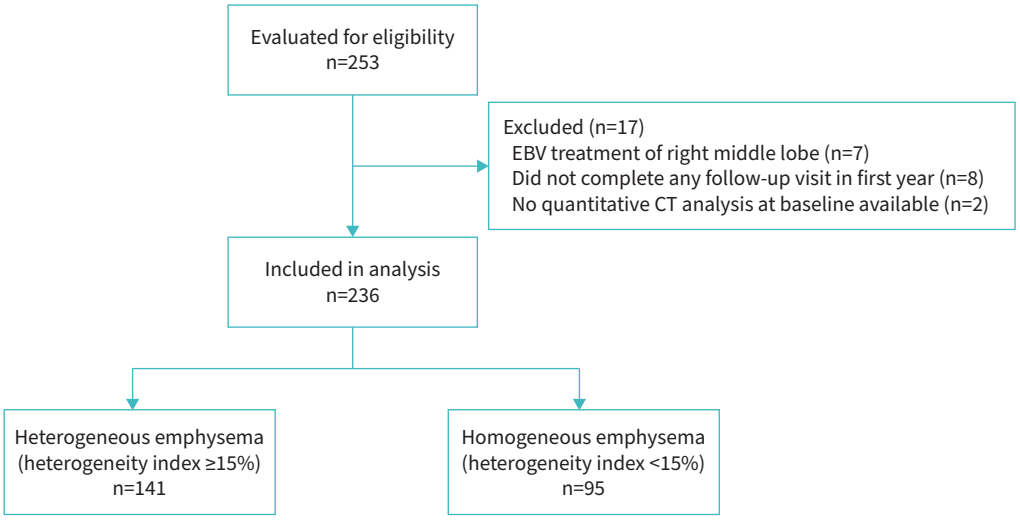

FIGURE 1 Patient flow diagram. EBV: endobronchial valve; CT: computed tomography.

TABLE 1 Baseline characteristics

	Overall	Heterogeneous[#]	Homogeneous[¶]	p-value
Patients	236	141	95	
Female	175 (74)	101 (72)	74 (78)	0.354
Age, years	62.5±7.3	62.4±7.5	62.7±7.0	0.728
BMI, kg·m^{-2}	24±4	24±4	23±4	**0.049**
Smoking, pack-years (n=235)	39 (28–49)	39 (27–46)	40 (28–53)	0.140
6MWD, m (n=235)	323±94	326±87	318±103	0.519
SGRQ, total score (n=229)	57±13	57±13	58±12	0.580
FEV_1, L	0.73±0.21	0.77±0.22	0.66±0.18	**<0.001**
FEV_1, % pred	27±8	28±8	25±6	**0.001**
RV, L (n=234)	4.92±1.09	4.91±1.14	4.94±1.03	0.828
RV, % predicted (n=234)	252±50	249±54	257±43	0.268
RV/TLC ratio, % (n=234)	64±7	64±6	65±7	0.069
D_{LCO}, % pred (n=207)	36±11	37±11	35±11	0.171
Target lobe quantitative CT analysis				
Volume, L	1.72 (1.50–2.13)	1.81 (1.56–2.29)	1.64 (1.41–1.96)	**0.003**
Destruction, $\%LAA_{-950insp}$	48±10	52±10	43±7	**<0.001**
Air trapping, $\%LAA_{-856exp}$ (n=205)	81 (76–85)	83 (80–86)	77 (70–80)	**<0.001**
Perfusion, %	13 (10–18)	12 (10–15)	17 (13–20)	**<0.001**
Ipsilateral lobe quantitative CT analysis				
Volume, L	1.64 (1.40–1.97)	1.61 (1.39–1.86)	1.72 (1.45–2.02)	**0.038**
Destruction, $\%LAA_{-950insp}$	28±11	22±8	36±8	**<0.001**
Air trapping, $\%LAA_{-856exp}$ (n=205)	57±15	52±14	66±11	**<0.001**
Perfusion, %	32±8	34±8	29±7	**<0.001**
Heterogeneity index	21±14	30±11	7±5	**<0.001**

Data are presented as n, n (%), mean±SD or median (interquartile range), unless otherwise stated. The heterogeneous and homogeneous subgroups were compared using the t-test or Mann–Whitney U-test for continuous variables and Chi-squared tests for categorical variables. Bold type represents statistical significance. BMI: body mass index; 6MWD: 6-min walk distance; SGRQ: St George's Respiratory Questionnaire; FEV_1: forced expiratory volume in 1 s; RV: residual volume; TLC: total lung capacity; D_{LCO}: diffusion capacity of lungs for carbon monoxide; CT: computed tomography; $LAA_{-950insp}$: low attenuation areas <−950 HU on the inspiratory CT scan; $LAA_{-856exp}$: low attenuation areas <−856 HU on the expiratory scan. [#]: heterogeneity index ⩾15%; [¶]: heterogeneity index <15%.

outcomes, the strength of the associations increased over time. The strongest associations were found between the heterogeneity index and change in RV at the 6-month (ρ=−0.308, p<0.001) and 12-month (ρ=−0.409, p<0.001) follow-up visits. When the analyses were repeated using only the data from patients who completed all three follow-up visits (n=142), no substantial differences were observed (supplementary table E2).

Heterogeneity index showed associations to pre-treatment target and ipsilateral lobe characteristics, especially destruction of the target (ρ=0.576, p<0.001) and ipsilateral lobes (ρ=−0.750, p<0.001), air trapping of the target (ρ=0.630, p<0.001) and ipsilateral lobes (ρ=−0.538, p<0.001) and perfusion of the

TABLE 2 Spearman's correlation coefficients between heterogeneity index and change in treatment response parameters

	6-week follow-up		6-month follow-up		12-month follow-up	
	ρ	p-value	ρ	p-value	ρ	p-value
ΔFEV_1, %	0.232	**<0.001**	0.270	**<0.001**	0.357	**<0.001**
ΔRV, %	−0.164	**0.018**	−0.308	**<0.001**	−0.409	**<0.001**
ΔSGRQ total score, %	−0.114	0.102	−0.262	**<0.001**	−0.300	**<0.001**
Δ6MWD, %	ND	ND	0.201	**0.007**	0.265	**<0.001**

Bold type represents statistical significance. Δ: change between baseline and follow-up; FEV_1: forced expiratory volume in 1 s; RV: residual volume; SGRQ: St George's Respiratory Questionnaire; 6MWD: 6-min walk distance; ND: not done.

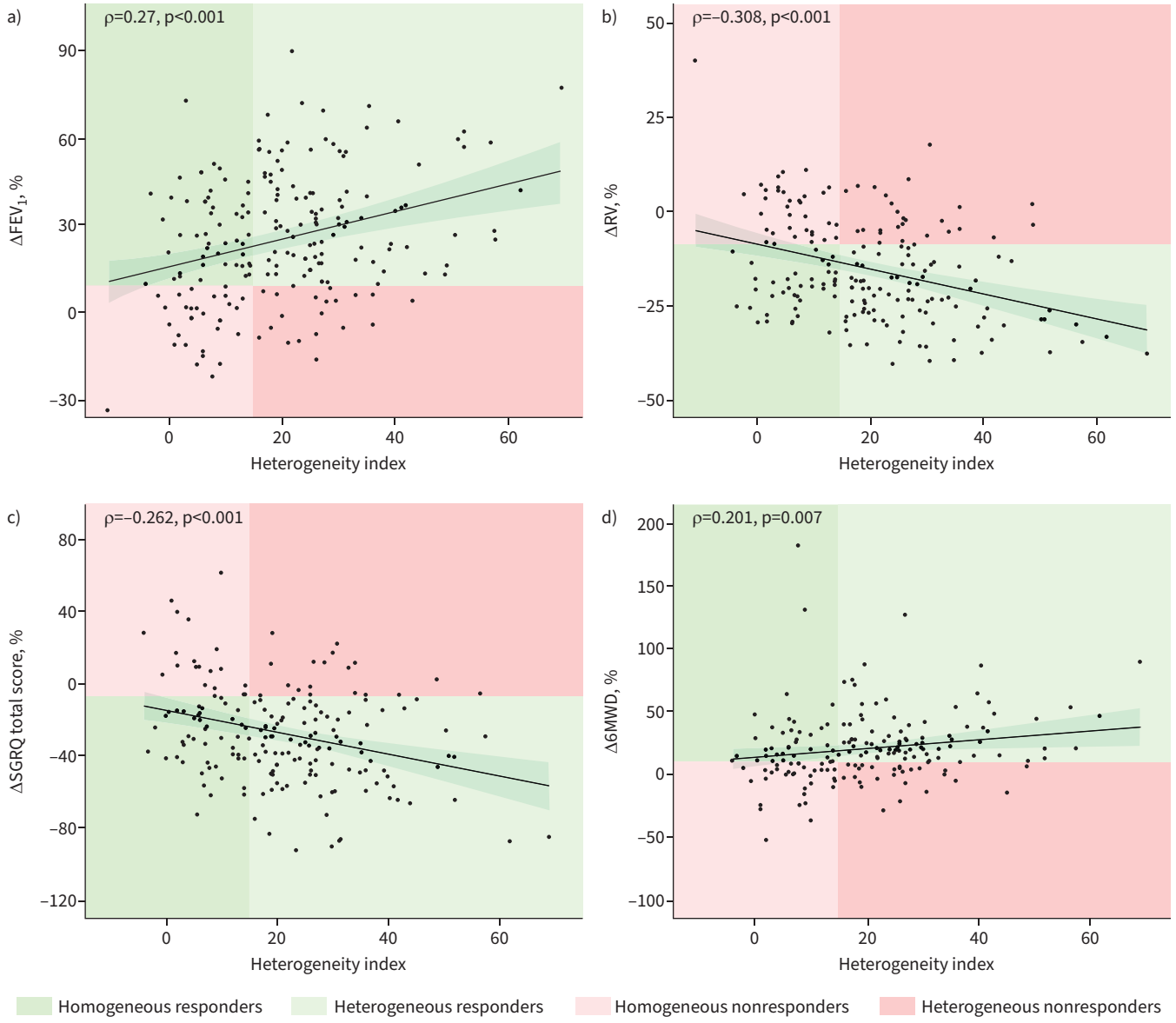

FIGURE 2 Scatterplots and fitted regression line (95% CI) depicting the association between the heterogeneity index and relative change (Δ) in a) forced expiratory volume in 1 s (FEV_1), b) residual volume (RV), c) total score on St George's Respiratory Questionnaire (SGRQ) and d) 6-min walk distance (6MWD), all 6 months after endobronchial valve treatment. The colour blocks indicate the categorisation of emphysema into homogeneous (heterogeneity index <15%) and heterogeneous (heterogeneity index ⩾15%) and the categorisation into responders (change reaches the minimal important difference threshold) or nonresponders.

target lobe (ρ=−0.537, p<0.001) (supplementary figure E4). Furthermore, there were significant, but weak, associations between the heterogeneity index and change in ipsilateral lobe volume (ρ=0.210, p=0.001), ipsilateral lung volume (ρ=−0.248, p<0.001) and QCT-derived total lung volume (ρ=−0.266, p<0.001) (supplementary figure E5).

Heterogeneous and homogeneous emphysema subgroups

Both the heterogeneous and homogeneous groups showed significant improvements in FEV_1, RV and SGRQ total score compared to their pre-treatment values up to the 12-month follow-up visit (figure 3 and supplementary table E3). The significant improvement in 6MWD persisted up to the 12-month follow-up visit in the heterogeneous subgroup, but in the homogeneous subgroup this improvement only persisted up to the 6-month follow-up visit.

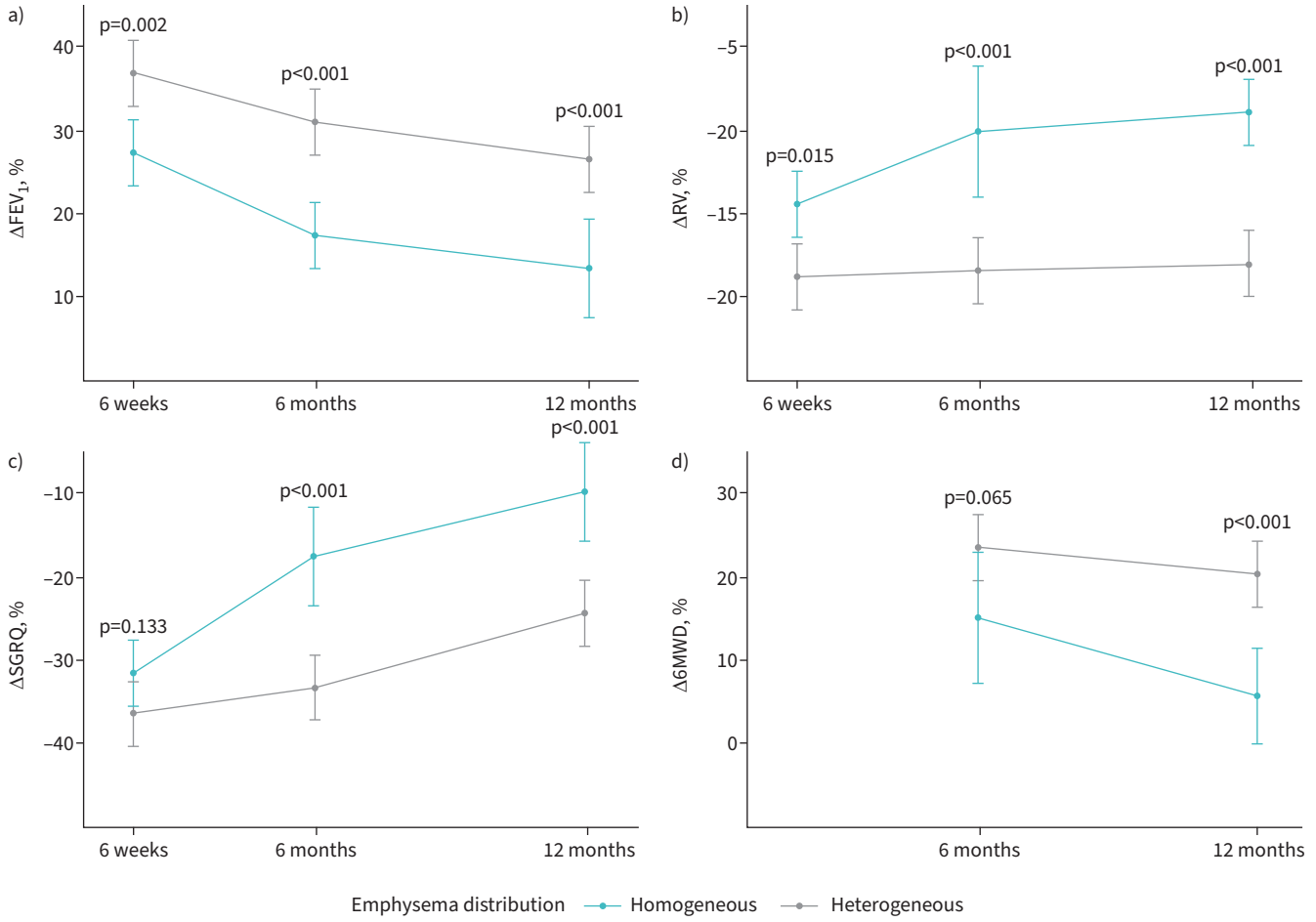

FIGURE 3 Changes in clinical outcomes after endobronchial valve treatment (mean, 95% CI) in the heterogeneous (heterogeneity index ⩾15%) and homogeneous (heterogeneity index <15%) subgroups. Relative change (Δ) in a) forced expiratory volume in 1 s (FEV_1), b) residual volume (RV), c) total score on St George's Respiratory Questionnaire (SGRQ) and d) 6-min walk distance (6MWD) (not assessed at 6-weeks follow-up). p-values indicate the between-group difference and are calculated using the t-test.

The magnitude of improvement in all outcome parameters was higher in the heterogeneous group compared to the homogeneous group (figure 3 and supplementary table E3). The between-group difference was significant for FEV_1 and RV at all included follow-up visits, for reduction in SGRQ total score at 6- and 12-month follow-up and for improvement in 6MWD at the 12-month follow-up.

The responder rates were higher in the heterogeneous than in the homogeneous subgroup, although the difference in response rate was not significant for RV at 6 weeks post-treatment, and for SGRQ total score at 6 weeks and 6 months post-treatment (figure 4). Despite the higher number of responders in the heterogeneous subgroup, more than half of the homogeneous patients were responders on all treatment outcomes, except for SGRQ and 6MWD at 12-month follow-up, which showed responder rates of 46% and 42%, respectively. There was no difference in the number of technically successful treatments, which is reflected by a similar number of patients reaching the MID for target lobe volume reduction (figure 4).

Predictive ability of the heterogeneity index

The ROC curves for heterogeneity index to predict responders 6 months after EBV treatment are shown in figure 5. The predictive ability of the heterogeneity index was low and similar for the different responder variables: FEV_1 (AUC=0.667), RV (AUC=0.644), SGRQ (AUC=0.578) and 6MWD (AUC=0.618).

Discussion

In this study, we found that heterogeneity index is not meaningful to predict a clinically meaningful response to EBV treatment, but is a possible indicator for the magnitude of response where a more

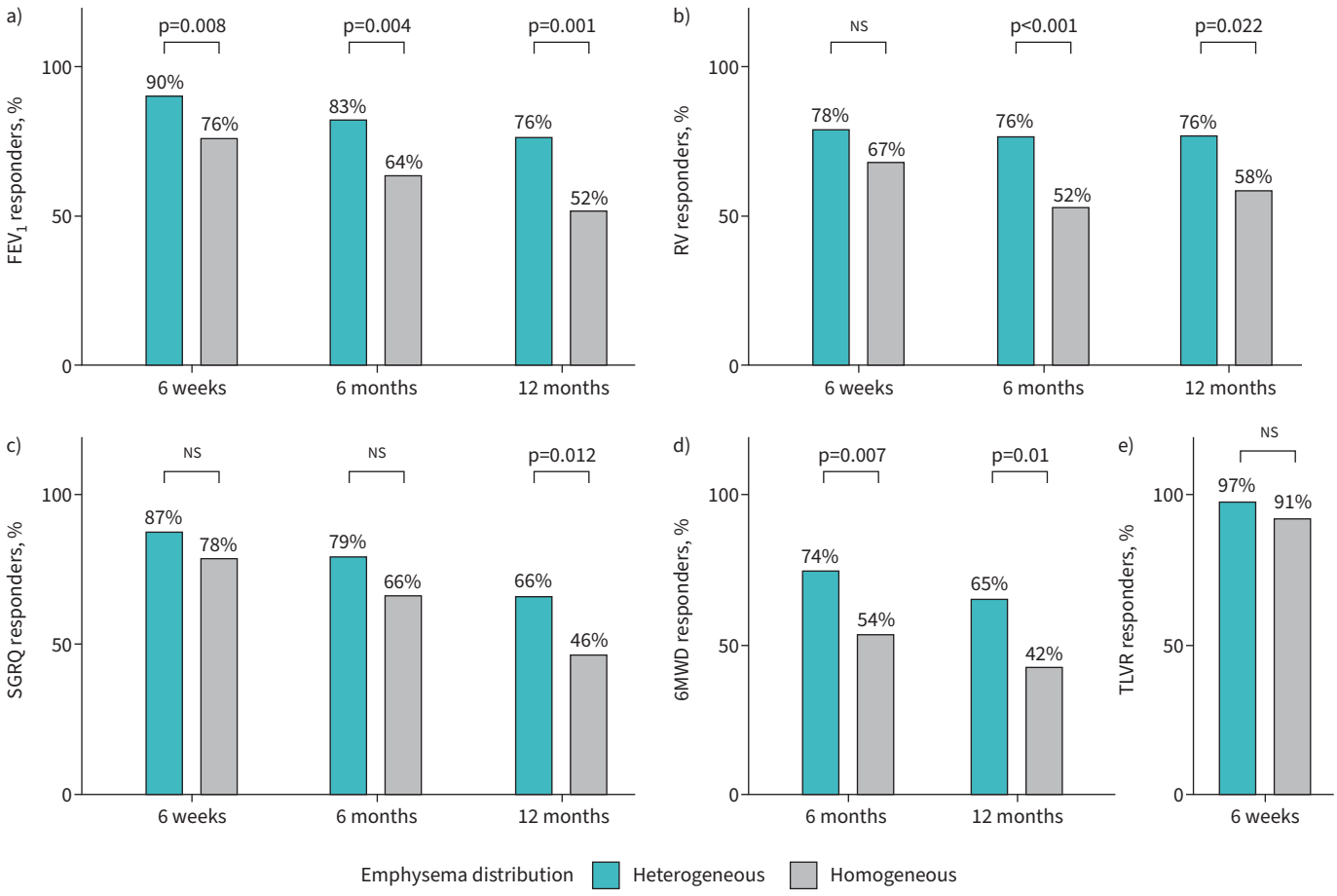

FIGURE 4 Percentage of responders in the heterogeneous (heterogeneity index ⩾15%) and homogeneous (heterogeneity index <15%) subgroups for a) forced expiratory volume in 1 s (FEV_1), b) residual volume (RV), c) total score on St George's Respiratory Questionnaire (SGRQ), d) 6-min walk distance (6MWD) and e) target lobe volume reduction (TLVR). NS: nonsignificant.

heterogeneous emphysema distribution (*i.e.* a higher heterogeneity index) was associated with greater improvements in pulmonary function, exercise capacity and quality of life. However, the strength of all these associations was weak-to-moderate and heterogeneity index showed a low predictive ability for the distinction between responders and nonresponders.

Nowadays, EBV treatment is an established treatment option for patients with advanced emphysema and severe hyperinflation that can result in meaningful improvements in clinical outcomes. Even when the treatment is technically successful, there is a large interpatient variability in response, which is probably the result of a combination of factors. Increasing the knowledge on which factors influence this variability in clinical outcome would be helpful for patient selection, but also for establishing realistic patient expectations before treatment. Our results suggest that the degree of emphysema heterogeneity between the targeted and ipsilateral nontargeted lobe is one of the factors that contributes to the magnitude of the treatment effect, where patients with a more heterogeneous distribution have greater improvements in FEV_1, RV, 6MWD and SGRQ and possibly a longer-lasting effect compared to patients with a more homogeneous distribution.

The positive influence of a higher degree of emphysema heterogeneity on the response to EBV treatment has a number of possible explanations. When looking at the target lobe, we found that a higher heterogeneity index was associated with more destruction, more air trapping and a lower perfusion of this lobe. Air trapping showed the strongest association with heterogeneity index, which could suggest that in patients with a more heterogeneous distribution, the target lobe has a greater negative contribution to the present hyperinflation and subsequently on respiratory mechanics and functional limitations [20]. If so, treating this lobe will lead to larger improvements. For the ipsilateral nontargeted lobe, the opposite was

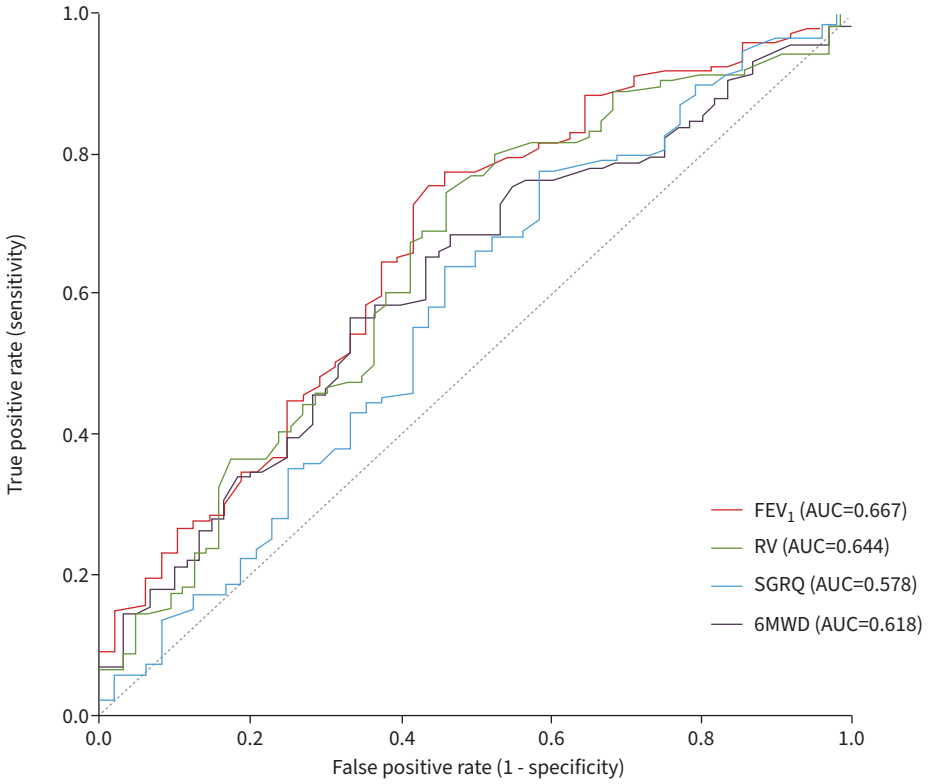

FIGURE 5 Receiver operator characteristic curves depicting the ability of the heterogeneity index to distinguish responders and nonresponders based on change (Δ) in forced expiratory volume in 1 s (FEV_1), residual volume (RV), St George's Respiratory Questionnaire (SGRQ) and 6-min walk distance (6MWD) 6 months after endobronchial valve treatment. A patient is defined as responder when the change in the specific variable exceeds the minimal important difference (MID). The following MID thresholds were used: $\Delta FEV_1 \geqslant 10\%$, $\Delta RV \leqslant -8.6\%$, $\Delta SGRQ \leqslant -7.1\%$ and $\Delta 6MWD \geqslant 10\%$. AUC: area under the curve.

found. For this lobe a higher heterogeneity index was associated with less destruction, less air trapping and, to a lower extent, a higher perfusion. This shows that the remaining lung tissue of the treated lung is less affected by emphysema in patients with a more heterogeneous distribution compared to patients with a more homogeneous distribution. After EBV treatment this remaining lung tissue will have more space and expectantly the perfusion to this tissue will increase due to hypoxic pulmonary vasoconstriction in the region of the treated lobe due to its collapse, both having a positive influence on change in functional limitations after treatment [21].

Another possible explanation for the lower treatment response in patients with a lower heterogeneity index and thus more homogeneous emphysema distribution might be excessive compensatory hyperinflation of the ipsilateral nontargeted lobe. When the target lobe loses volume there is a volume redistribution, primarily consisting of a volume increase of the ipsilateral lobe and, to a lesser extent, of the contralateral lung [22–24]. Since the ipsilateral lobe is generally more affected by emphysema in patients with a lower heterogeneity index, this lobe might be more susceptible to overexpansion. Although some degree of volume increase of the ipsilateral lobe is desirable, overexpansion of this lobe will lead to minimal or no nett reduction in hyperinflation with consequently less clinical improvements [22]. Interestingly, we observed the opposite: a higher heterogeneity index resulted in a greater relative increase in volume of the ipsilateral lobe. However, we did observe a higher relative reduction in volume on the treated side and a higher nett reduction of volume in patients with a higher heterogeneity index, suggesting that, at least up to 6 weeks after treatment, ipsilateral lobe overexpansion does not explain the higher treatment response in patients with a more heterogeneous emphysema distribution. We did observe that the strength of the association between the heterogeneity index and improvement in clinical outcomes increased over time. It could be hypothesised that overexpansion of the ipsilateral lobe develops over time and thereby contributes to the more rapid loss of treatment effect in patients with a more homogeneous emphysema distribution.

Unfortunately, we do not perform regular chest CT scans after 6-weeks follow-up, but it would be interesting to investigate in the future.

Currently, no widely accepted heterogeneity index cut-off is available to define the emphysema distribution as either homogeneous or heterogeneous. However also based on our results, we believe a hard cut-off is not of added value, at least in the context of EBV treatment. In previous EBV studies, a 15% heterogeneity index cut-off was most frequently used to divide emphysema distribution. In line with the results of the IMPACT study [4], we found that a large group of patients with "homogeneous emphysema" can significantly benefit from EBV treatment up to 12-month follow-up. Moreover, in the majority of these patients, their improvements reach the minimal important difference threshold. Furthermore, we found that the heterogeneity index only has a predictive ability of 60–67% to classify responders and nonresponders. Thus, using a heterogeneity index cut-off value as a selection criterion will result in undertreatment of patient with a more homogeneous emphysema distribution that can experience clinically meaningful improvements. Since these patients have limited to no other treatment options, we believe that heterogeneity index alone should not be used as a selection criterion for EBV treatment.

This study has some limitations. First, all the patients included in this study received EBV treatment and with that were deemed eligible for treatment after discussion in our multidisciplinary board. It is likely that a number of patients were not found eligible for EBV treatment mainly on the basis of a homogeneous distribution of emphysema, but in combination with other factors such as low destruction, low air trapping and/or a high perfusion of the potential target, which probably influenced our results. The patient selection procedure in our hospital has been described before [25] and is in accordance to the EBV expert statement from 2017 [26]. However, this mainly shows that appropriate patient and target lobe selection is key, and that a homogeneous distribution alone does not result in treatment failure. Furthermore, we calculated the heterogeneity index as the difference in destruction between the target and ipsilateral lobe, including the right middle lobe, if applicable. However, there are multiple ways to calculate this index [15]. Using a different definition for heterogeneity could have resulted in different findings. However, the method we used is the most commonly used within EBV studies, and we believe that it is unlikely that using a different definition would have resulted in finding a cut-off value below which patients show no response to EBV treatment or that would have resulted in substantially different findings. Additionally, to quantify the amount of destruction different thresholds are defined of which below −910 HU and −950 HU are the most frequently used. Using a different threshold value could affect the calculated heterogeneity index. However, we showed that there is an almost perfect association between the heterogeneity indices which are calculated based on the −910 HU and −950 HU destruction thresholds.

In conclusion, the heterogeneity of emphysema distribution between the target and ipsilateral lobe influences the degree of improvement in pulmonary function, exercise capacity and quality of life after EBV treatment. Generally, it could be stated that the more heterogeneous the distribution, the more pronounced the improvements. Presumably, for the most part, this can be explained by the presence of a more pronounced treatment target lobe in patients with a higher heterogeneity index with more destruction, more air trapping and less perfusion, not only compared to the ipsilateral lobe, but also compared to target and ipsilateral lobes of patients with a lower heterogeneity index. However, heterogeneity index has a low predictive ability for treatment response, meaning that also patients with a low heterogeneity index can experience clinically meaningful improvement. Therefore, we believe heterogeneity index should not be used as a decisive patient selection criterion for EBV treatment, but should be weighed in the context of all other relevant patient and target lobe characteristics when deciding on a patient's treatment eligibility. Furthermore, the findings of this study can be used to inform patients, especially those with a more homogeneous emphysema distribution, on expected outcomes.

Provenance: Submitted article, peer reviewed.

Author contributions: All authors made substantial contributions to the conceptualisation or design of the work, or the acquisition, analysis and/or interpretation of the data used in this work. S.A. Roodenburg wrote the first draft of the manuscript. K. Klooster, D-J. Slebos and J.E. Hartman critically revised the work. All authors approved the final version submitted for publication and agree to be accountable for all aspects of the published work.

Conflict of interest: K. Klooster reports support for attending meetings from PulmonX, outside the context of the submitted work. D-J. Slebos reports grants or contracts, consulting fees, honoraria, support for attending meetings and receiving materials from PulmonX, PneumRx and Nuvaira, and grants or contracts from Free Flow Medical, all outside the context of the submitted work. S.A. Roodenburg and J. Hartman report no conflicts of interest.

References

1 World Health Organization (WHO). Chronic Obstructive Pulmonary Disease (COPD). 2022. www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd). Date last updated: 16 March 2023.
2 Snider GL, Kleinerman J, Thurlbeck WM, *et al.* The definition of emphysema. Report of a National Heart, Lung, and Blood Institute, Division of Lung Diseases workshop. *Am Rev Respir Dis* 1985; 132: 182–185.
3 Ju J, Li R, Gu S, *et al.* Impact of emphysema heterogeneity on pulmonary function. *PLoS One* 2014; 9: e113320.
4 Valipour A, Slebos D-J, Herth F, *et al.* Endobronchial valve therapy in patients with homogeneous emphysema. Results from the IMPACT study. *Am J Respir Crit Care Med* 2016; 194: 1073–1082.
5 National Emphysema Treatment Trial Research Group. Patients at high risk of death after lung-volume-reduction surgery. *N Engl J Med* 2001; 345: 1075–1083.
6 Fishman A, Martinez F, Naunheim K, *et al.* A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* 2003; 348: 2059–2073.
7 Sciurba FC, Ernst A, Herth FJF, *et al.* A randomized study of endobronchial valves for advanced emphysema. *N Engl J Med* 2010; 363: 1233–1244.
8 Herth FJF, Noppen M, Valipour A, *et al.* Efficacy predictors of lung volume reduction with Zephyr valves in a European cohort. *Eur Respir J* 2012; 39: 1334–1342.
9 Klooster K, ten Hacken NHT, Hartman JE, *et al.* Endobronchial valves for emphysema without interlobar collateral ventilation. *N Engl J Med* 2015; 373: 2325–2335.
10 Kemp SV, Slebos D-J, Kirk A, *et al.* A multicenter randomized controlled trial of zephyr endobronchial valve treatment in heterogeneous emphysema (TRANSFORM). *Am J Respir Crit Care Med* 2017; 196: 1535–1543.
11 Criner GJ, Sue R, Wright S, *et al.* A multicenter randomized controlled trial of zephyr endobronchial valve treatment in heterogeneous emphysema (LIBERATE). *Am J Respir Crit Care Med* 2018; 198: 1151–1164.
12 Davey C, Zoumot Z, Jordan S, *et al.* Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFi study): a randomised controlled trial. *Lancet* 2015; 386: 1066–1073.
13 Hartman JE, Criner GJ, Moore WH, *et al.* HRCT characteristics of severe emphysema patients: interobserver variability among expert readers and comparison with quantitative software. *Eur J Radiol* 2021; 136: 109561.
14 Koster TD, Klooster K, van Dijk M, *et al.* Perfusion measured with HRCT-approximated perfusion is comparable to SPECT/CT for patients with severe COPD. *Eur Respir J* 2022; 60: Suppl. 66, 3800.
15 Theilig D, Doellinger F, Poellinger A, *et al.* Comparison of distinctive models for calculating an interlobar emphysema heterogeneity index in patients prior to endoscopic lung volume reduction. *Int J Chron Obstruct Pulmon Dis* 2017; 12: 1631–1640.
16 Hartman JE, Ten Hacken NH, Klooster K, *et al.* The minimal important difference for residual volume in patients with severe emphysema. *Eur Respir J* 2012; 40: 1137–1141.
17 Welling JB, Hartman JE, Ten Hacken NH, *et al.* The minimal important difference for the St George's Respiratory Questionnaire in patients with severe COPD. *Eur Respir J* 2015; 46: 1598–1604.
18 Puhan MA, Mador MJ, Held U, *et al.* Interpretation of treatment changes in 6-minute walk distance in patients with COPD. *Eur Respir J* 2008; 32: 637–643.
19 Welling JBA, Hartman JE, van Rikxoort EM, *et al.* Minimal important difference of target lobar volume reduction after endobronchial valve treatment for emphysema. *Respirology* 2018; 23: 306–310.
20 Dos Santos Yamaguti WP, Paulin E, Shibao S, *et al.* Air trapping: the major factor limiting diaphragm mobility in chronic obstructive pulmonary disease patients. *Respirology* 2008; 13: 138–144.
21 Dunham-Snary KJ, Wu D, Sykes EA, *et al.* Hypoxic pulmonary vasoconstriction. *Chest* 2017; 151: 181–192.
22 Wienker J, Darwiche K, Wälscher J, *et al.* Clinical impact of compensatory hyperinflation of the nontreated adjacent lobe after bronchoscopic lung volume reduction with valves. *Int J Chron Obstruct Pulmon Dis* 2022; 17: 1523–1536.
23 Coxson HO, Nasute Fauerbach PV, Storness-Bliss C, *et al.* Computed tomography assessment of lung volume changes after bronchial valve treatment. *Eur Respir J* 2008; 32: 1443–1450.
24 Brown MS, Kim HJ, Abtin FG, *et al.* Emphysema lung lobe volume reduction: effects on the ipsilateral and contralateral lobes. *Eur Radiol* 2012; 22: 1547–1555.
25 Welling JBA, Hartman JE, Augustijn SWS, *et al.* Patient selection for bronchoscopic lung volume reduction. *Int J Chron Obstruct Pulmon Dis* 2020; 15: 871–881.
26 Slebos DJ, Shah PL, Herth FJ, *et al.* Endobronchial valves for endoscopic lung volume reduction: best practice recommendations from expert panel on endoscopic lung volume reduction. *Respiration* 2017; 93: 138–150.