ORIGINAL RESEARCH

Clinical Impact of Compensatory Hyperinflation of the Nontreated Adjacent Lobe After Bronchoscopic Lung Volume Reduction with Valves

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Background: Bronchoscopic lung volume reduction (BLVR) with endobronchial valves (EBV) can be a successful treatment for end-stage emphysema patients. The reduction of hyperinflation enhances ventilatory mechanics and diaphragm function. Understanding predictors for treatment success is crucial for further improvements.

Purpose: The aim of this study was to assess the effect of the target lobe volume reduction (TLVR) in relation to the ipsilateral lung volume reduction (ILVR), affected by the compensatory expansion of the adjacent lobe, on the outcome after BLVR with valves.

Patients and Methods: The volumetric relationship of ILVR% to TLVR%, addressed as *Reduction Ratio* (*R*), was recorded in 82 patients and compared to changes in lung function, physical performance and quality of life. A small value for *R* implies a relatively low volume reduction of the ipsilateral lung (ILVR) compared to the volume reduction of the target lobe (TLVR). Additionally, the minimal clinically important difference (MCID) for *R* was calculated.

Results: Patients with a smaller *Reduction Ratio* (*R* <0.2) showed minor improvements at the 3 months follow-up compared to patients with $R \geq 0.2$ (mean changes of 39 mL (5.8%), –395 mL (–4.9%) and 96 mL (7.1%) versus 231 mL (33%), –1235 mL (–20%) and 425 mL (29%) in the forced expiratory volume in 1s (FEV_1), residual volume (RV) and inspiratory vital capacity (IVC), respectively, and –3 m and 0 points versus 20.4 m and –3.4 points in the 6-minute-walking-distance (6MWD) and COPD assessment test (CAT) score respectively). With a combined value of 0.185, a MCID for *R* was calculated with established anchors (FEV_1, RV, and 6MWD) for emphysema patients.

Conclusion: Extensive compensatory hyperinflation of the adjacent non-treated lobe after BLVR results in decreased ILVR, which is responsible for a lack of meaningful improvements in ventilatory mechanics and clinical outcome, despite technically successful lobe volume reduction.

Keywords: emphysema, ipsilateral lung volume, reduction ratio, volume shift

Introduction

The pathological changes in patients with chronic obstructive pulmonary disease (COPD) result in impaired gas exchange along with an inefficient ventilation. Among others, tobacco inhalation is the major noxious agent which causes a progress in emphysematous destruction of the lung tissue, leading to hyperinflation and reduced ventilatory function. In addition to an optimal medical and supportive treatment, endoscopic procedures for lung volume reduction have become an integral part of the treatment. Bronchoscopic lung volume reduction (BLVR) with valves is a frequently used approach. Unidirectional valves are placed in the airways of the most emphysematous inflated sections of the lung to prevent air from entering while allowing trapped air to escape. This non-surgical method is intended to reduce hyperinflation, thereby improving diaphragm function and ventilatory mechanics. The VENT-Study in 2010 was the first major prospective randomized clinical trial (RCT) that has been designed to show the efficacy of endobronchial valves (EBV) for patients with end-stage emphysema. Although the idea behind this approach seemed to

be promising, the clinical improvements were unsatisfactory and only modest changes in lung function have been recorded. A subgroup analysis quickly revealed missing fissure integrity and collateral ventilation as the reason for the insufficient results.[1] Further reasons for poor clinical outcomes were connected to the (persisting) complications of the interventional valve placement, with pneumothorax being the most frequently recorded complication.[2] In patients with persistent air leaks, the implanted valves need to be removed and other volume reduction approaches should be assessed. Other complications and reasons for therapy failure include incomplete lobar occlusion, severe COPD exacerbations, mucus accumulation, pneumonia or the formation of granulation tissue due to irritating contact with the mucosal tissue.[3]

A careful patient selection and the elaborate pre-interventional diagnostic routine improves the therapy response and the safety of endoscopic lung volume reduction with valves. Multiple RCTs showed statistically significant and clinically meaningful improvements.[4–7]

If patients treated with BLVR achieved a radiological secured significant volume reduction but did not clinically benefit from the treatment, the sheer progression of COPD was held accountable.[8] Recent studies showed that BLVR can lead to a volume shift from the target lobe, which results in a compensatory hyperinflation of the neighboring, non-treated lobe(s).[1,3,9,10] With that considered, another explanation for a missing therapy response might be the overexpansion and redistribution of emphysema to the non-treated neighboring lobe(s). This eventually prevents a significant volume reduction of the ipsilateral lung and therefore improvements of ventilatory mechanics and diaphragm function are compromised. The clinical impact of the ipsilateral lung volume reduction (ILVR) depending on the extent of the compensatory hyperinflation of the non-treated lobe was not yet described. The aim of this study is to examine this relationship and the effect on the outcome after bronchoscopic lung volume reduction (BLVR) with valves, determined by changes in lung function and volumes, physical activity and quality of life.

Materials and Methods
Patients
In this retrospective single-center trial, we evaluated patients with end-stage emphysema, who were treated with one-way endobronchial valves (Zephyr© Endobronchial Valve; Pulmonx, Inc., Redwood City, CA, USA) in our tertiary care center from January 2015 to December 2020. For the analysis of volumetric changes after valve placement, only patients who received a post-interventional high resolution quantitative computed tomography (QCT) were enrolled. Patients were excluded if the target lobe volume reduction (TLVR) was below the minimal clinically important difference (MCID) of 563 mL determined by Welling et al.[11] All pre- and post-interventional QCTs were analyzed and changes were compared with the same analysis software (StratX© software, Pulmonx, Inc.).

Patients were considered for BLVR with valves after exhaustion of medical and supportive treatment and the plethysmography revealed a forced expiratory volume in 1s (FEV_1) <40% predicted and a RV >200% predicted. While the value for FEV_1 corresponds with the severity of obstruction, the RV is a measure of hyperinflation. Prior to valve implantation, each patient went through a standardized diagnostic protocol to ensure optimal preconditions and to identify the target lobe with the highest degree of emphysema. Collateral ventilation is determined by a two-step process. QCT analysis is used to evaluate fissure completeness together with lobe volumes and heterogeneity of the emphysema. Additionally, the Chartis catheter-based system (Pulmonx, Inc.) was applied as a physical measurement to increase the sensitivity of excluding collateral ventilation. Furthermore, a perfusion scan, an echocardiography to exclude cardiac insufficiency and a 6-minute-walking-test (6MWT) to examine the physical fitness were performed. The quality of life was determined with the COPD assessment test (CAT). The joint review of lung function together with the functional assessment enhances patient selection and ensures that primarily end-stage emphysema patients with severely impaired lung function are treated with EBVs and clinically less compromised patients, with a lower chance to benefit from BLVR, are not considered. All cases were then individually discussed in a multidisciplinary board consisting of (interventional) pneumologists, thoracic surgeons and radiologists for an optimal treatment decision. Before BLVR, all patients at our center underwent pulmonary rehabilitation and ceased smoking for at least 6 months, which was verified by normal serum carboxyhemoglobin (COHb) and urinary cotinine levels.

After valve placement, patients were regularly admitted to the intensive care unit for 24h and then monitored for another two days for potential complications. Follow-ups were scheduled at 30 days, 90 days and 6 months after implantation to repeat pulmonary function tests, 6MWT and the CAT. A HR-CT was performed at 90 days for a post-interventional QCT analysis. In synopsis of all results, the overall treatment success can thus be objectified.

This study was conducted in accordance with the Declaration of Helsinki and the study protocol was approved by the local Ethics Committee of the University of Duisburg-Essen (22-10510-BO). All patients provided written, informed consent for BLVR treatment.

Volumetric Quantification

The pre- and post-interventional lobar volumes were evaluated with a QCT analysis software (StratX© software, Pulmonx, Inc.). In the process of patient selection prior to valve placement, a HR-CT scan is done and uploaded anonymously to a cloud-based platform. Next to the analysis of the fissure integrity, the resulting "lung report" displays degree and heterogeneity of emphysema. Furthermore, precise information on the lobar volumes is provided. It is also recognized, when complete atelectasis is achieved due to bronchial occlusion. Main reasons for unsuccessful or non-functioning QCT analysis were missing slices, incompatible or poor CT-resolution or postprocedural pneumothorax, present when the scan was performed. We examined the change of volumes of the target lobe and the adjacent ipsilateral lobe(s), to determine the target lobe volume reduction (TLVR) and the (overall) ipsilateral lung volume reduction (ILVR). Additionally, the proportion of the TLVR towards the ILVR (ILVR%/TLVR%), addressed as the *Reduction* Ratio *(R)*, was calculated to identify an over-compensatory hyperinflation of the adjacent lobe(s) and then compared to the outcome after BLVR. The smaller the value for *R*, the more volume is shifted to the overcompensating adjacent lobe(s), indicating a low ILVR. Figure 1 shows an explanatory schematic illustration. The contralateral lung was also analyzed for changes in lobe volumes.

Outcome Variables

With the QCT analysis reports, we got information about the volumetric changes of the treated ipsilateral and contralateral lung with target and adjacent lobe volume reduction, so that their *Reduction* Ratio *R* could be calculated. We compared this ratio with the outcome after BLVR, which is determined by the changes in pulmonary function (FEV_1, RV, and IVC), physical performance (6MWT) and quality of life (CAT).

Pulmonary function was assessed with body plethysmography, the 6MWT was performed according to the standard routine with information on oxygen saturation, usage of walking aid devices and supplemental oxygen consumption. The COPD assessment test is based on a questionnaire.

Statistical Analysis

We performed a group-differentiated analysis with an a priori defined cut-off for *R* at the median at 0.2 to compare an equal number of patients in each group [n = 41 for <0.2 versus n = 41 for ≥0.2]. Changes of outcome parameters from baseline after 3 months were analyzed within each group with a paired-samples *t*-test in case of parametric distribution of data and a Wilcoxon signed-rank test in case of non-parametric distribution. Differences between groups were analyzed with an independent-samples *t*-test in case of parametric distribution of data and a Mann–Whitney *U*-test in case of non-parametric distribution. Variables were tested with the Shapiro–Wilk-Test for parametric distribution. A MCID responder analysis for FEV_1, RV and 6MWD is compared using chi squared test. Since we introduced the quotient *R* for our investigation, we also calculated a MCID based on our data. With a linear regression analysis and a receiver operating characteristic (ROC)-analysis, two anchor-based methods were used with established anchors: (1) ΔFEV_1 – 100 mL, (2) ΔRV – 310 mL and (3) $\Delta 6MWD \geq 26$ m.[12–15] The final MCID was then defined as the mean value from the three anchor-parameters of both methods. A statistically significant correlation >0.3 between the anchors and *R* is desirable. Correlations between *R* and outcome variables were calculated with the non-parametric Spearman correlation coefficient (r_s). A p-value <0.05 was considered as statistically significant. Statistical analyses and graph preparation were performed using SPSS version 23 (IBM, New York, NY, USA) and Prism version 8 (GraphPad, San Diego, CA, USA).
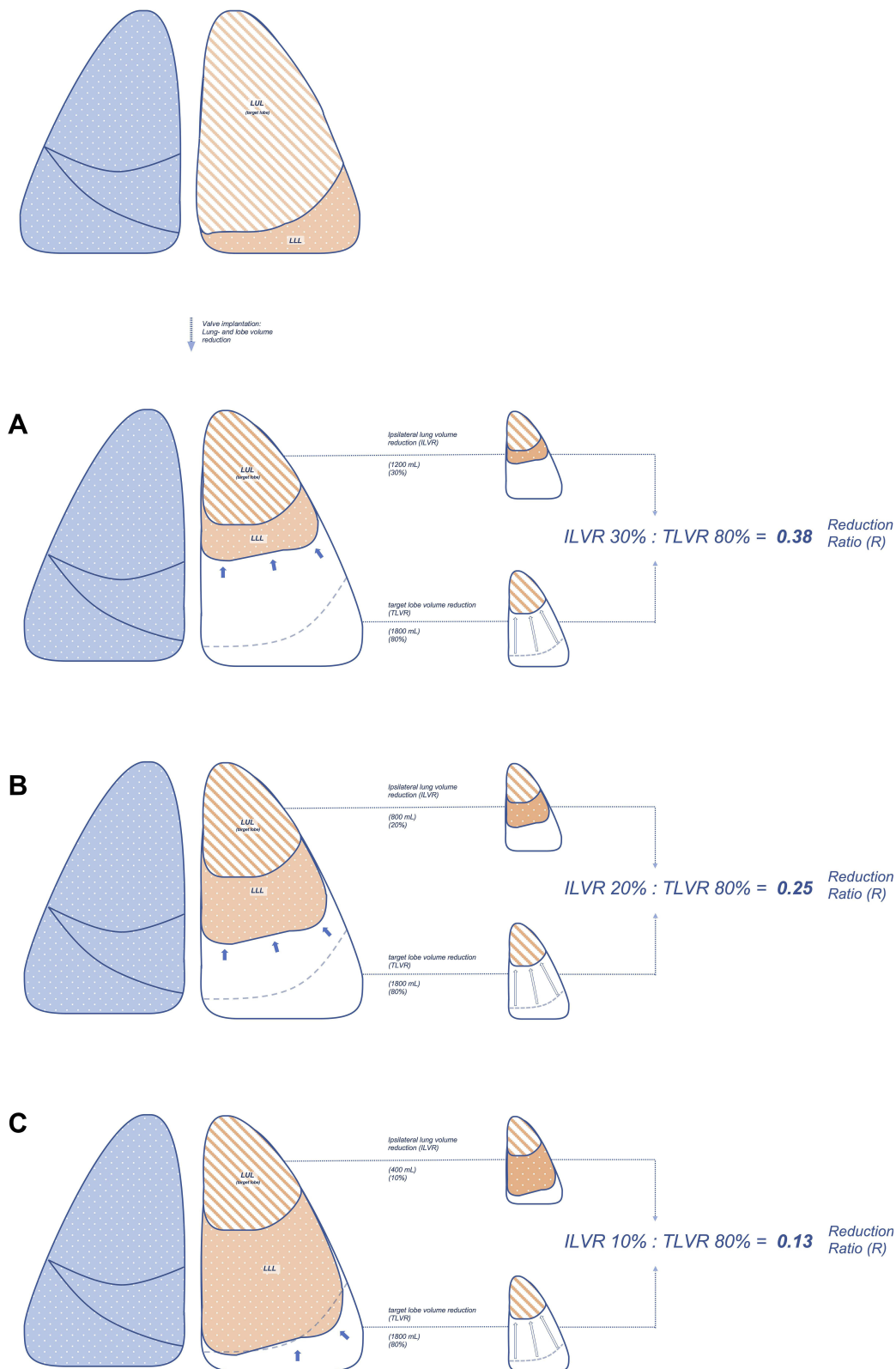
Figure 1 Schematic illustration of the assumed pathophysiology showing examples of the same target lobe volume reduction (TLVR in %) ⬜ in relationship to different ipsilateral lung volume reductions (ILVR in %) ⬜ for the calculation of the *Reduction Ratio (R)*.
Notes: The relationship between the ipsilateral lung volume reduction (ILVR in %) and the target lobe volume reduction (TLVR in %) is obtained from the data. This provides a computable value, addressed as *Reduction Ratio (R)*, which can be compared to clinical changes from the interventional treatment. Thereby the effect of a potential compensatory hyperinflation of the non-treated adjacent lobe(s) can be elucidated and quantified. Subfigures (**A**), (**B**) and (**C**) show different exemplary proportions of ILVR to TLVR. A smaller ILVR relative to the TLVR as displayed in (**C**) leads to a lower *Reduction Ratio (R)*, indicating an over-compensating hyperinflation of the neighboring lobe(s).
Abbreviations: LUL, left upper lobe; LLL, left lower lobe; ILVR, ipsilateral lung volume reduction; TLVR, target lobe volume reduction.

Results

From 2015 to 2020, 146 patients treated with endobronchial valves at our clinic were identified with available and valid post-interventional HR-CT scans. In 36 cases, a QCT-analysis was not feasible: 5 patients were excluded due to pneumothorax at the time of the scan, 4 patients received scans with inconsistent slice spacing and another 27 patients had scans with missing slices. For the remaining 110 patients a post-BLVR QCT-analysis was available. From this group, 28 patients were missing the TLVR-MCID of 563 mL so that we finally included 82 patients (average age 62 years, 56 female and 26 male) in our analysis (Figure 2).

The baseline demographic and clinical data are displayed in Table 1. All patients were treated with zephyr endobronchial valves and had complete occlusion of the treated lobe. The left lung was treated in the majority of cases with the left upper lobe (LUL) being the most frequently targeted (n=61 [74%], LUL = 36 and LLL = 25), while in the right lung the lower lobe (RLL) was targeted more often (n = 21 [26%], RUL = 9, RML = 1, RLL = 11).
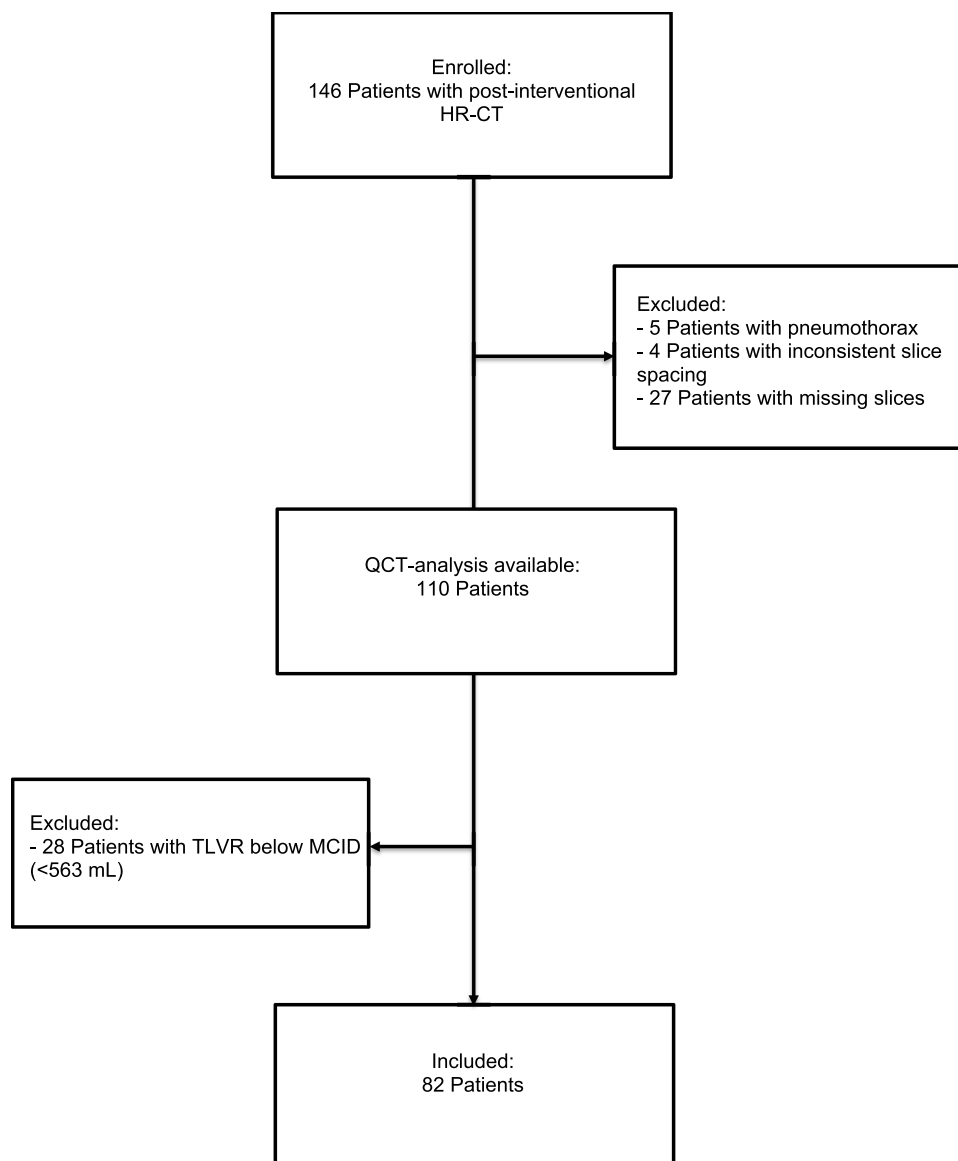

Figure 2 Patient selection flow chart.
Abbreviations: HR-CT, high resolution computed-tomography; QCT, quantitative computed-tomography; TLVR, target lobe volume reduction; MCID, minimal clinically important difference.

Table 1 Demographic and Clinical Characteristics at Baseline

Variables	
Patients, n	82
Gender, female/male	56/26
Age, years	62 ± 6.9
Weight, kg	66 ± 14.8
Height, cm	169 ± 8.8
Smoking history, pack-years	36 ± 14
FEV$_1$	
Liters	0.76 ± 0.177
% predicted	28.3 ± 7.57
RV	
Liters	5.73 ± 1.28
% predicted	267 ± 47.9
IVC	
Liters	2.15 ± 0.67
% predicted	63.1 ± 17.4
TLV, milliliters	1703 ± 474
ILV, milliliters	3368 ± 886
6MWD, meters	314 ± 72
CAT score (n=42)	23.4 ± 5.71

Notes: Values are mean ± standard deviation, or number of patients (%).
Abbreviations: CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; ILV, ipsilateral lung volume; IVC, inspiratory vital capacity; RV, residual volume; TLV, target lobe volume; 6MWD, 6-min walking distance.

After 3 months, the patients showed general clinical improvements in lung function, physical performance and quality of life at the follow-up examination indicating an overall benefit from BLVR treatment (ΔFEV$_1$ 135 mL ± 168 mL, ΔRV − 763 mL ± 1250 mL, ΔIVC 258 mL ± 493 mL, Δ6MWD 8.9 m ± 54 m, ΔCAT score − 1.3 points ± 5.2 points).

Concerning the patient's safety, a pneumothorax occurred in 12 cases (14.6%), while a mild exacerbation was recorded in 7 patients (8.5%). Chest tube placement was necessary in 9 cases. There was no case of valve displacement or migration and complications were manageable with no necessity of valve removal. There were 7 patients where the formation of new bullae was radiologically recorded within the adjacent lobe. In 5 of those 7 cases, the upper lobe was treated.

The group differentiated analysis based on the R value showed significant differences for changes of clinical parameters within and between the groups, displayed in Table 2 and Figure 3 respectively. For R <0.2, statistically non-significant improvements with mean changes of 5.8% (39 mL), − 4.9% (− 395 mL) and 7.1% (96 mL) for FEV$_1$, RV and IVC, respectively, as well as − 3 m and 0 points for the 6MWT and CAT score were recorded. Patients with R values ≥0.2 showed a better treatment response with significant mean changes of 33% (231 mL), − 20% (− 1235 mL) and 29% (425 mL) for FEV$_1$, RV and IVC, respectively, and improvements in the 6MWT and CAT score were 20.4m and − 3.4 points. The pneumothorax rate in patients with extensive hyperinflation was twice as high as in those with modest expansion (8 cases for R <0.2 and 4 cases for R ≥0.2).

Regarding the QCT-based volumetric analysis, all patients showed a fissure completeness of >95% for the treated lobe. The volumetric measurements showed significant differences of the post-interventional adjacent lobe(s) volume (ALV) and the ipsilateral lung volume (ILV), since R is the quotient of the percentage change of these volumes. However, the target lobe volume (TLV) and contralateral lung volume (CLV) were not significantly different from each other, while also all pre-interventional lobe and lung volumes showed no differences (Table 4). The lower lobes had a higher mean value for R than the upper lobes (0.25 vs 0.17) and showed a tendency for a better clinical outcome. Yet the target lobe destination, whether it was the right lung with an additional middle lobe versus the left lung or upper versus lower lobe, had no statistically significant influence on the outcome.

Table 2 Changes in Lung Function and Exercise Capacity 90 Days After Bronchoscopic Lung Volume Reduction with Valves

Reduction Ratio (R)	<0.2 (n=41)			≥0.2 (n=41)		
	Pre-Implant (Baseline)	Post-Implant (3-Months Follow-Up)	P-value	Pre-Implant (Baseline)	Post-Implant (3-Months Follow-Up)	P-value
FEV₁						
Value in liters ± SD	0.79 ± 0.18	0.83 ± 0.19		0.74 ± 0.17	0.97 ± 0.24	
% change	–	+ 5.8	0.012		+ 33.2	<0.001
RV						
Value in liters ± SD	5.75 ± 1.38	5.35 ± 1.2		5.73 ± 1.21	4.50 ± 1.07	
% change	–	– 4.9	n.s.		– 20.4	<0.001
IVC						
Value in liters ± SD	2.30 ± 0.64	2.39 ± 0.65		2.01 ± 0.68	2.43 ± 0.63	
% change	–	+ 7.1	n.s.		+ 28.8	<0.001
6MWD						
Value in meters ± SD	316 ± 66	313 ± 84		315 ± 80	335 ± 84	
Change in meters	–	– 3	n.s.		+ 20.4	0.016
CAT score (n=42)						
Points ± SD	22.3 ± 1.44	22.4 ± 1.22		24.25 ± 5.62	20.88 ± 5.92	
Change in points	–	0	n.s.		– 3.37	0.009

Notes: Changes were analyzed with a paired-samples *t*-test in case of parametric distribution of data and a Wilcoxon signed-rank test in case of non-parametric distribution.
Abbreviations: CAT, COPD assessment test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; IVC, inspiratory vital capacity; n.s., not statistically significant; RV, residual volume; SD, standard deviation; 6MWD, 6-min walking distance.

Furthermore, a significant correlation of the designated quotient with changes of pulmonary function tests and physical performance could be shown and are displayed with scatter plots in Figure 4 (r_s=0.661, r_s= – 0.477 and r_s=0.434 for ΔFEV_1, ΔRV, ΔIVC and r_s=0.306 for Δ6MWD). There was no significant correlation with the change of the CAT score.

Similarly, the ipsilateral lung volume reduction (ILVR) itself also showed significant correlation with all changes in pulmonary function tests and physical performance. The volume change of the target lobe (TLVR), on the other hand, did not significantly correlate with any outcome variable.

With all correlations being above the threshold of 0.3, we were able to calculate the MCID with both methods that were described. For the linear regression, the anchor values were entered in the equation to derive the MCID. The ROC-analysis provided sufficient areas under the curve (AUCs) for all anchors (0.844, 0.813 and 0.686 for FEV₁, RV and 6MWT, respectively). As presented in Table 5, the MCIDs range from 0.168 to 0.2, with a combined value of 0.185.

A responder analysis, with regard to achieving the established MCIDs (ΔFEV_1 >100 mL, ΔRV >310 mL and Δ6MWD >25 m), revealed that patients with $R \geq 0.2$ showed a superior response (78%, 85% and 54% vs 24%, 41% and 27%, respectively, shown in Table 4).[12–14]

The data analysis that we performed with the percentage changes for the quotient R (ILVR% to TLVR%) was repeated for different relationships of volumetric changes, such as ILVR (mL) to TLVR (mL) and ΔALV (% and mL) to TLVR (% and mL). From these, the ratio of percentage changes showed the best correlation with the outcome variables.

Discussion

In this study, we analyzed the influence of ipsilateral lung volume reduction in relation to the compensatory hyperinflation of the adjacent lobe on the outcome after bronchoscopic lung volume reduction with valves. After a significant TLVR, patients with severe volume shift to the neighboring non-targeted lobe showed less ipsilateral lung volume reduction (ILVR), which resulted in a poor clinical outcome, compared to those with only modest compensatory volume increase of the adjacent lobe. This was confirmed by comparing the newly introduced *Reduction Ratio* (*R*), which is the quotient of the percentage change of ILVR to TLVR, with the changes in lung function, physical performance, and quality of life. As already mentioned in the results, the ILVR itself, which is a more direct and simple volumetric value than the quotient *R*, also showed a significant correlation. Nevertheless, we decided in favor of the quotient *R*, since it
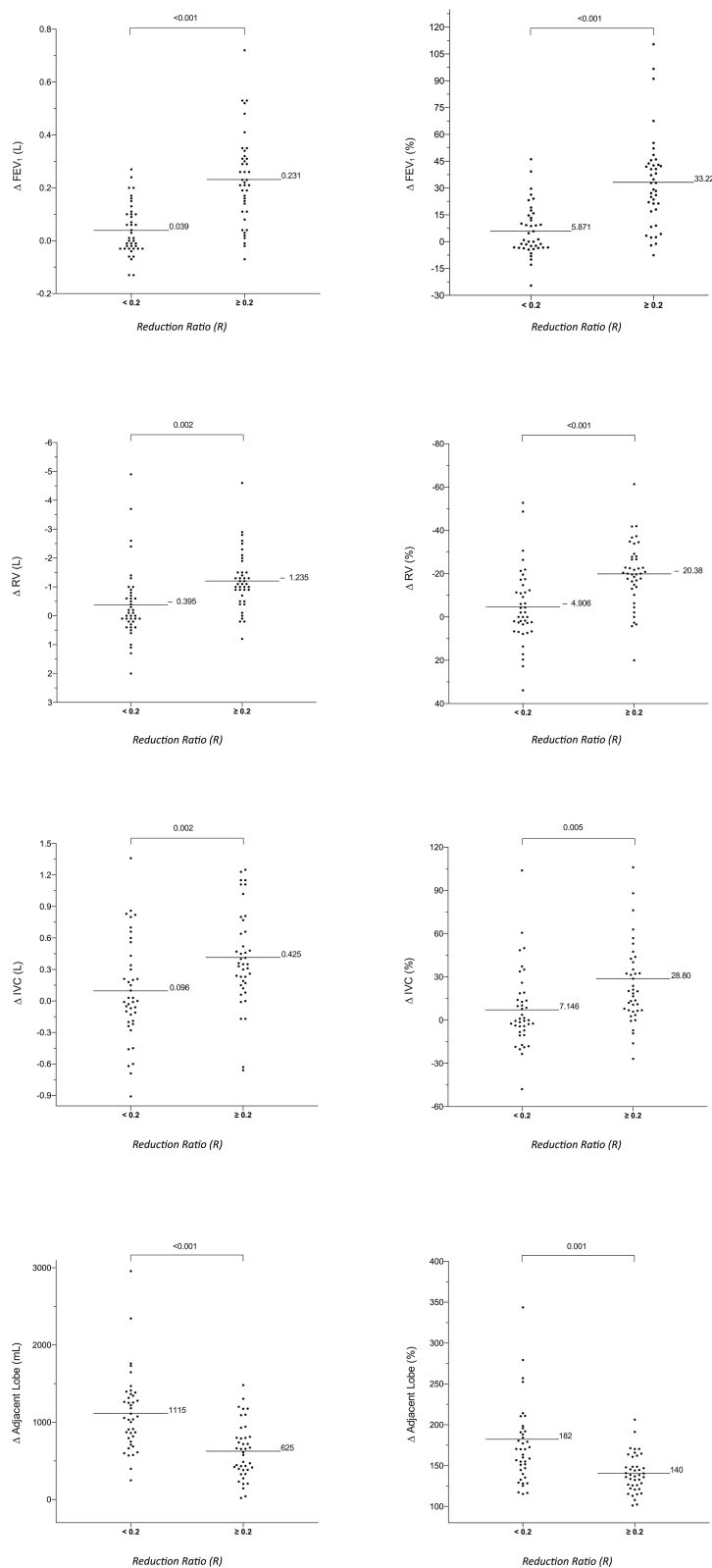
Figure 3 Dot plots of changes in lung function, adjacent lobe volume and physical activity and associated mean values compared to *Reduction Ratio* (R).
Notes: Difference between groups was analyzed with an independent-samples *t*-test in case of parametric distribution of data and a Mann–Whitney *U*-test in case of non-parametric distribution.
Abbreviations: FEV1, forced expiratory volume in 1 s; IVC, inspiratory vital capacity; RV, residual volume.

Table 3 Target Lobe Distribution

Variables	Reduction Ratio (R)		P-value
	<0.2 (n=41)	≥0.2 (n=41)	
Lobe treated			
Left upper lobe (LUL), n	22	14	n.s.
Left lower lobe (LLL), n	9	16	n.s.
Right upper lobe (RUL), n	6	3	n.s.
Right middle lobe (RML), n	1	0	n.s.
Right lower lobe (RLL), n	3	8	n.s.
Upper lobes, n	28	17	0.026
Lower/middle lobe(s), n	13	24	0.026
Right lung, n	10	11	n.s.
Left lung, n	31	30	n.s.

Notes: Difference between groups was analyzed with the Chi squared test.
Abbreviations: n.s., not statistically significant.

Table 4 Changes in Lung Volumes and MCID-Responder Analysis 90 Days After Bronchoscopic Lung Volume Reduction with Valves

Variables	Reduction Ratio (R)		P-value
	<0.2 (n=41)	≥0.2 (n=41)	
Target Lobe Volume (TLV)			
Pre-implant, mL ± SD	1643 ± 469	1763 ± 477	n.s.
Post-implant, mL ± SD	247 ± 398	314 ± 453	n.s.
Δ mL (TLVR)	− 1396 ± 463	− 1449 ± 560	n.s.
Δ % (TLVR)	− 84.9 ± 21	− 82.5 ± 23	n.s.
Ipsilateral Lung Volume (ILV)			
Pre-implant, mL ± SD	3318 ± 677	3419 ± 744	n.s.
Post-implant, mL ± SD	3038 ± 680	2551 ± 624	0.001
Δ mL (ILVR)	− 280 ± 205	− 868 ± 353	<0.001
Δ % (ILVR)	− 8.5 ± 6.2	− 25.3 ± 8.4	<0.001
Adjacent Lobe(s) Volume (ALV)			
Pre-implant, mL ± SD	1688 ± 602	1610 ± 458	n.s.
Post-implant, mL ± SD	2804 ± 609	2236 ± 643	<0.001
Δ mL	1116 ± 504	626 ± 356	<0.001
Δ %	82.3 ± 72	40.5 ± 23	0.001
Contralateral Lung Volume (CLV)			
Pre-implant, mL ± SD	3441 ± 634	3416 ± 748	n.s.
Post-implant, mL ± SD	3643 ± 678	3627 ± 894	n.s.
Δ mL	202 ± 261	211 ± 310	n.s.
Δ %	6.2 ± 8.6	5.8 ± 8.3	n.s.
Δ FEV_1 >100 mL[†], n (%)	10 (24)	32 (78)	<0.001*
Δ RV >310 mL[†], n (%)	17 (41)	35 (85)	<0.001*
Δ 6MWD >25 m[†], n (%)	11 (27)	22 (54)	0.012*

Notes: Difference between groups was analyzed with an independent-samples t-test in case of parametric distribution of data and a Mann–Whitney U-test in case of non-parametric distribution. *Chi squared test. [†]Minimal clinically important difference. Δ, mean change from baseline to follow up.
Abbreviations: FEV_1, forced expiratory volume in 1 s; n.s., not statistically significant; RV, residual volume; 6MWD, 6-min walking distance.
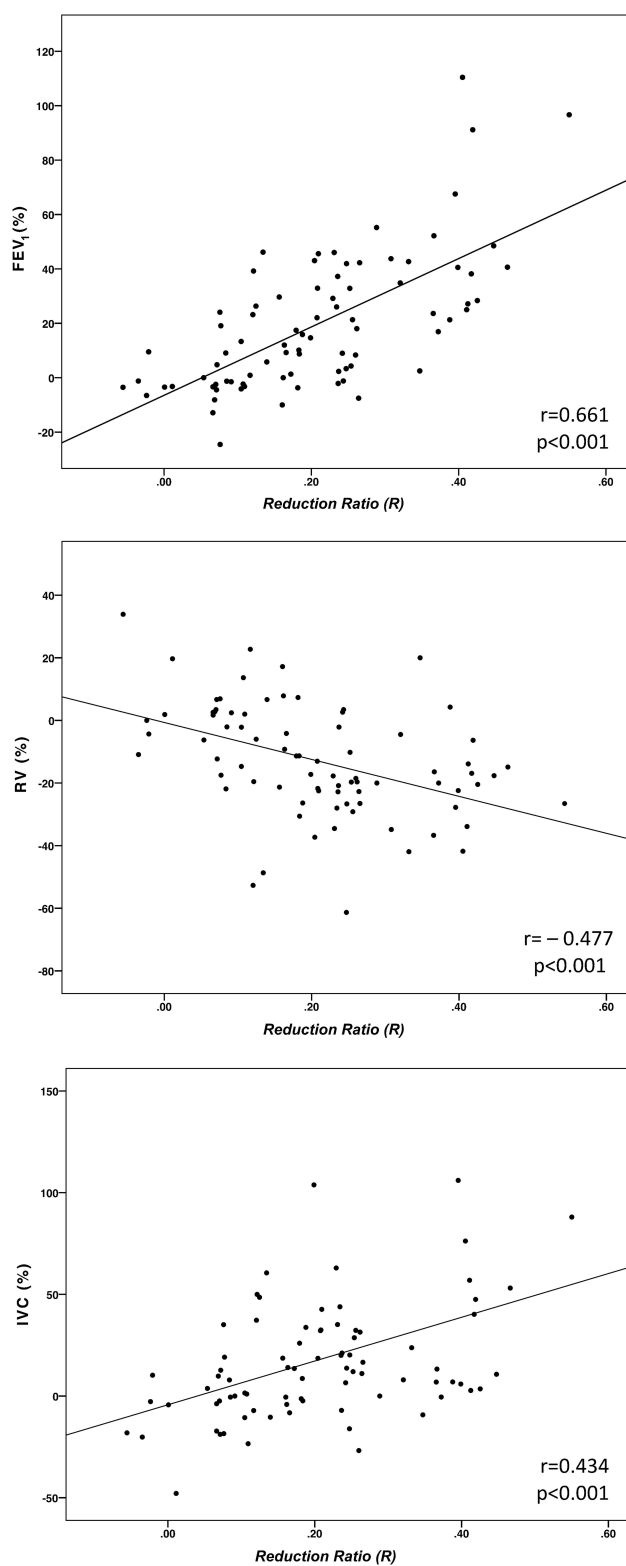
Figure 4 *R* in relation to changes in lung function showing significant correlations.
Abbreviations: FEV1, forced expiratory volume in 1 s; IVC, inspiratory vital capacity; RV, residual volume.

Table 5 Minimal Clinically Important Difference for R

Method	Anchor	MCID
Linear Regression Analysis		
	FEV$_1$	0.190
	RV	0.168
	6MWD	0.20
ROC-Analysis		
	FEV$_1$	0.188
	RV	0.173
	6MWD	0.190
Combined		**0.185**

Abbreviations: FEV1, forced expiratory volume in 1 s; MCID, minimal clinically important difference; RV, residual volume; 6MWD, 6-min walk distance.

better represents the impact of the compensatory hyperinflation of the adjacent lobe and the role of ventilatory mechanics.

Beyond alveolar destruction and reduced gas exchange, emphysema has been shown to severely impair respiratory mechanics and elastic recoil. Lung volume reduction, either by bronchoscopic or surgical means, enhances the ventilatory function by improving diaphragm motion range and achieving greater mechanical efficiency of the inspiratory muscles.[16,17] For patients who received BLVR, an association between the TLVR and clinical outcome parameters has been identified before and it could be shown that patients with TLVR >50% achieved better results than those with a TLVR <50%.[18] Therefore, different MCIDs for the target lobe volume reduction from 563 mL up to 890–1070 mL have been postulated to support a clinically meaningful improvement.[11,19] In our observation, all patients showed average target lobe reduction volumes that were above the MCIDs, while there was no significant difference between the two groups (–1396 mL [R <0.2] vs –1449 mL [R ≥0.2], Table 4). Yet only patients who developed a significant TLVR *associated with an ipsilateral lung volume reduction (ILVR)* to a similar extent showed a clinical benefit in this study. TLVR alone, the volumetric scale (mL) and percentage value (%), was not significantly correlated with most outcome parameters and showed only poor significant correlation with the mean percentage change of RV (r_s=0.227).

Coxson et al examined lung volume changes after BLVR of the upper lobes with intrabronchial valves (IBV) and demonstrated a volume redistribution to the non-treated lobe. While a significant target (upper) lobe volume reduction is described, there was no significant change of the total lung volume and the patients from this investigation showed no clinical improvement in pulmonary function after BLVR with valves. However, it has to be mentioned that collateral ventilation and fissure integrity was not fully understood at that time.[10] In addition to the major volume shift of to the non-treated adjacent lobe, Brown et al also showed that minor quantities are redistributed to the contralateral lobe. Furthermore, a TLVR in this trial also resulted in an overall volume reduction of the whole lung. The results though were not compared to their clinical impact.[9] Although we observed volume redistribution to the adjacent lobe(s) in nearly all cases, there was no significant volume shift to the contralateral lung.

We recorded a pneumothorax rate of 14.6% (12 cases). The volume shift from the treated to the neighboring lobe is a potential explanation for the occurrence of a pneumothorax after valve placement.[20] Our findings support this statement since the rate of pneumothorax in the group with extensive volume shift (R <0.2) is 20% (8 cases) and thus twice as high as in the group with modest volume shift with 10% (4 cases for R ≥0.2). Additionally, 7 patients (8.5%) developed a mild exacerbation after BLVR, evenly distributed to the two groups. There were no other, more severe complications, which might be explained due to the reason that cases, where valve removal could have been necessary, a QCT-analysis was not possible and therefore these cases were initially not included.

The calculation of the MCID should be ideally based on multiple approaches. With the ROC-analysis and the linear regression analysis, we used two anchor-based methods since these are the most direct and clinically related approaches. Distribution-based methods present a different way for MCID calculation. These approaches are more statistically based while not being disease, patient or clinically related.[21] In our observation, distribution-based methods were ineligible

since there is no feasible baseline value for R, being a quotient of a lobe to lung volume change. We divided the patients by a median-based cut-off value at 0.2, which is close to the calculated MCID of 0.185.

As displayed in Table 3 there is a significant difference ($p = 0.026$) of compensatory hyperinflation of the adjacent lobe comparing upper vs lower/middle lobes. With 28 versus 17 cases, most patients treated with valves in the upper lobes showed R values <0.2, meaning that there seems to be a higher chance for extensive volume shift and over-expansion of the adjacent lobe when the upper lobe volume is interventionally reduced. The mean R value for patients treated in the upper lobe was therefore significantly smaller than in patients treated in the lower lobe (Upper Lobes, n = 45, R=0.17; Lower Lobes, n = 37, R=0.25).
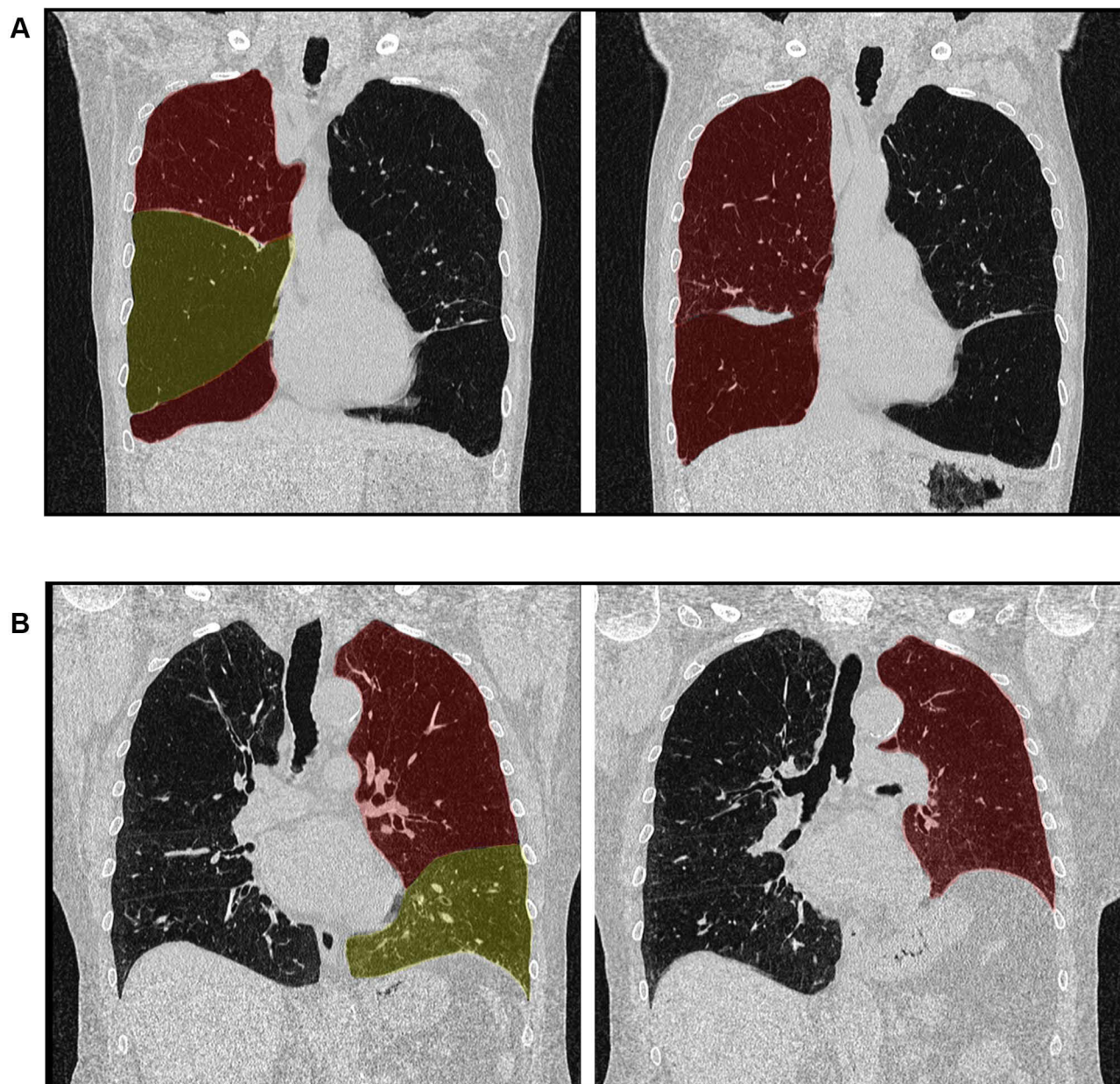
Figure 5 Representative exemplary CT images in the coronal plane of a patients with R <0.2 (**A**) and R ≥0.2 (**B**).
Notes: The target lobe is marked yellow, the non-treated neighboring lobes are marked in red. In both cases, a complete atelectasis of the target lobe was achieved. Subfigure A shows a patient with an R of 0.07: the volume is redistributed to the neighboring lobes and there is no shift of the diaphragm. In subfigure B, the R value is 0.4, with an evident upwards shift of the diaphragm.

From the clinical experience, there might be an explanatory pathophysiological relationship for this overrepresentation of the upper lobes. In some patients after BLVR in our center, we observed that the shrinking upper lobe drags the adjacent lower lobe upwards. In HR-CTs, strong adhesions between the two lobes were visible, so that the side of the lower adjacent lobe which faces the diaphragm stays in place and only the apical parts are pulled upwards, thus promoting the development of new emphysematous bullae. Due to the rapidity of this process, the adjacent lower lobe(s) has no time to reorganize within the pleural cavity when the diaphragm finally shifts upwards. In contrast, when the lower lobes are treated, the adjacent upper lobe is not pulled down, but the diaphragm is shifted upwards, so that there seems to be a lesser chance for new bullae to develop. In our patient cohort, we have seen seven cases after valve placement, where the volume shift led to new emphysematous bullae that have not been identified before. Five of these cases (71%) were recorded within the upper lobe, while two were in the lower lobes, which indicates a tendency towards the upper lobes. Valve placement within the upper lobe shows smaller R values and therefore seems to be connected to a higher probability of compensatory hyperinflation to the adjacent lobe. The clinical outcome, on the other hand, shows no statistically significant difference between upper and lower lobe, which is consistent with results described in recent studies.[22] Figure 5 shows representative CT images of a patient with an R <0.2 (A) compared to a patient with an $R \geq 0.2$ (B). In subfigure A, the volume of the middle lobe, which was treated with valves, redistributes to the neighboring lower and upper lobes so that the ipsilateral lung volume did not decrease and no diaphragmatic shift can be observed, even though a complete atelectasis was achieved. The corresponding R in this case is 0.07. The patient in subfigure B with an R of 0.4 is treated in the left lower lobe and achieves complete atelectasis together with an upwards shift of the diaphragm. Here, the non-treated upper lobe shows a modest increase in volume indicating that there was only a minor volume redistribution from the target lobe.

There are limitations to this study. First, this is a retrospective single-center investigation with a limited number of patients, therefore the results from our data must be confirmed in further research. Several QCT-analyses were not possible due to inconsistent or missing slices so that another 31 cases were not included. Furthermore, there is missing quality of life (CAT score) data in 40 cases. It would have been desirable to identify pre-interventional patient attributes that predict the likelihood of overinflation of the adjacent lobe prior to interventional valve placement. Except for the above-mentioned relationship to upper lobe treatment, no other baseline characteristics were significantly connected to the final extent of hyperinflation.

Conclusion

In this study, the influence of compensatory hyperinflation of the adjacent lobe was described and discussed. We compared the *Reduction Ratio (R)* to the outcome in order to get a better understanding of the respondence to BLVR treatment, especially in cases with no clinical improvements, even though there was a quantitatively secured significant target lobe volume reduction. An extensive compensatory hyperinflation of the neighboring non-treated lobe results in a reduced volume reduction of the ipsilateral lung, causing clinically insufficient improvements of ventilatory mechanics and clinical outcome.

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