Thieme

Selecting Patients for Lobar Lung Volume Reduction Therapy: What Quantitative Computed Tomography Parameters Matter?

Selektionskriterien für die Lungenvolumenreduktionstherapie: Welche Parameter der quantitativen Computertomografie sind relevant?

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ZUSAMMENFASSUNG

Ziel Vor endoskopischer Lungenvolumenreduktion (ELVR) ist die Evaluation der Emphysemverteilung mittels quantitativer Computertomografie (qCT) empfohlen. Ziel dieser retrospektiven Studie war festzustellen, welche qCT-Parameter das postinterventionelle Outcome am besten vorhersagen.
Material und Methoden Die präinterventionellen Computertomografien von fünfzig in unserer Institution technisch erfolgreich mit ELVR behandelten Patienten wurden quantitativ analysiert und mit prä- und postinterventionellen Lungenfunktionsuntersuchungen verglichen. Untersucht wurde die Relevanz der standardmäßig erhobenen qCT-Parameter, d. h. Gesamtlungenvolumen, Ziellappenvolumen, Emphysemindex der gesamten Lunge und des Ziellappens sowie Heterogenitätsindex. Mann-Whitney U-Test und logistische Regressionsanalyse wurden zur Identifikation derjenigen Parameter verwendet, die am besten einen Anstieg der FEV1 hervorsagten.
Ergebnisse Im Mann-Whitney U-Test unterschieden sich lediglich interlobärer Emphysemheterogenitätsindex (p = 0,008) und pulmonaler Emphysemindex (p = 0,022) signifikant zwischen Therapieansprechern und Therapieversagern. Die logistische Regressionsanalyse zeigte lediglich für den Heterogenitätsindex signifikante Unterschiede zwischen beiden Patientengruppen (p = 0,008). Gesamtlungenvolumen, Ziellappenvolumen, sowie die Emphysemindices der gesamten Lunge und des Ziellappens wiesen dort keine signifikanten Unterschiede auf.
Schlußfolgerungen Von allen bei der präinterventionellen qCT erhobenen Parametern scheint lediglich der interlobäre Heterogenitätsindex das klinische Outcome nach ELVR verlässlich vorauszusagen.

Kernaussagen
- Vor ELVR wird die Durchführung einer quantitativen CT empfohlen.
- Die Relevanz der qCT-Parameter ist weiterhin umstritten.
- Diese Studie bekräftigt, dass ausschließlich die Emphysemheterogenität einen relevanten Einfluss hat.

ABSTRACT

Purpose Evaluation of emphysema distribution with quantitative computed tomography (qCT) prior to endoscopic lung volume reduction (ELVR) is recommended. The aim of this study was to determine which of the commonly assessed qCT parameters prior to endoscopic lung volume reduction (ELVR) best predicts outcome of treatment.
Materials and Methods 50 patients who underwent technically successful ELVR at our institution were retrospectively analyzed. We performed quantitative analysis of the CT scans obtained prior to ELVR and carried out Mann-Whitney U-tests and a logistic regression analysis to identify the qCT parameters that predict successful outcome of ELVR in terms of improved forced expiratory volume in 1 second (FEV1).

Results In the Mann-Whitney U-test, the interlobar emphysema heterogeneity index (p = 0.008) and the pulmonary emphysema score (p = 0.022) showed a statistically significant difference between responders and non-responders. In multiple logistic regression analysis only the interlobar emphysema heterogeneity index (p = 0.008) showed a statistically significant impact on the outcome of ELVR, while targeted lobe volume, total lung volume, targeted lobe emphysema score and total lung emphysema score did not.

Conclusion Of all commonly assessed quantitative CT parameters, only the heterogeneity index definitely allows prediction of ELVR outcome in patients with advanced chronic obstructive pulmonary disease (COPD).

Key Points

- Quantitative CT is recommended prior to ELVR.
- The relevance of the obtained parameters from quantitative CT remains controversial.
- This study confirms that only the emphysema heterogeneity index has a definite impact.

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Introduction

Many studies have shown the therapeutic benefits of endoscopic lung volume reduction (ELVR) with placement of one-way endobronchial valves in patients with severe pulmonary emphysema [1 – 9] provided that there is no collateral ventilation of the targeted lobe [1, 10 – 13]. Total lobar occlusion is generally thought to yield better results than a segmental approach [14, 15]. Quantitative computed tomography (qCT) is increasingly being used to identify patients most likely to benefit from ELVR and to decide on the lobe to be treated to ensure the best outcome. However, little scientific evidence is available about the actual relevance of the parameters commonly determined by qCT, i. e., lung volume, targeted lobe volume, total lung emphysema score, targeted lobe emphysema score and interlobar emphysema heterogeneity. Several studies found interlobar emphysema heterogeneity to have an impact on the outcome of ELVR [1, 16] while others did not [8]. To our knowledge, to date no study has systematically investigated whether the total lung emphysema score or the targeted lobe emphysema score, while being intuitively relevant, allows prediction of the outcome of ELVR.

Therefore, the aim of this study was to elucidate the relevance of commonly obtained qCT parameters prior to ELVR in terms of the outcome of treatment assessed as improvement in forced expiratory volume in 1 second (FEV1). As proposed in the literature, we used a minimal clinically important difference (MCID) of 100 ml in FEV1 to distinguish between clinically successful and unsuccessful treatment [17].

Materials and Methods

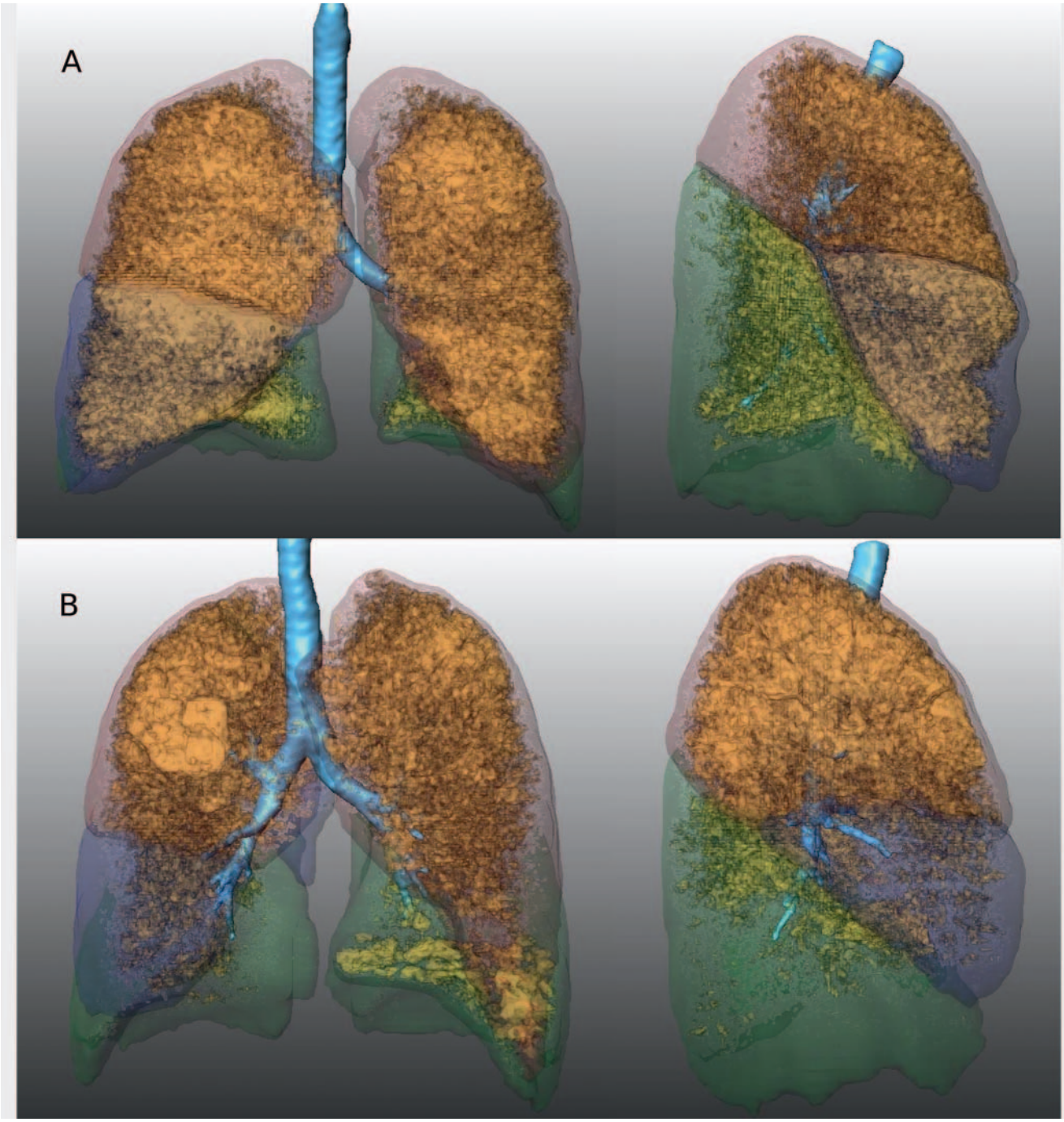
The study was approved by the local ethics committee (EA1/213/16).

Patient population

62 patients with advanced chronic obstructive pulmonary disease (COPD) and concomitant emphysema who underwent ELVR with one-way silicone Zephyr valves (Pulmonx, Redwood City, CA, USA) at our institution and received CT scans and lung function tests before and after treatment were included in our retrospective study. In this patient population, the targeted lobe for ELVR was selected on the basis of the visually assessed degree of emphysema, perfusion and the absence of collateral ventilation determined by the Chartis system (Pulmonx, Redwood City, CA, USA) as described in the study by Thomsen et al. [18]. As recommended by several investigators [14, 15], complete occlusion of the targeted lobe was performed in all study patients. To that end one-way silicone valves available in three sizes (4.0, 4.0-LP and 5.5) were inserted into the lobar or segmental bronchi according to the patient's individual lung anatomy until the entire lobe was occluded. On average, 3.8 valves were inserted via a flexible delivery catheter. Following the literature, we classified a targeted lobe volume reduction of more than 350 ml as technically successful treatment [11]. Patients without technically successful treatment were excluded from further analysis, leaving a total of 50 patients for final analysis. This was done to avoid bias due to technical problems such as leakage around the valves or valve dislocation, which would obscure the results, as the aim of the study was not to evaluate the aptness of the bronchoscopist or the material but rather to find out which lobe would yield the best outcome when treated with valves provided that valve placement went well. An example of two different patients with successful valve implantation is shown in ▶ **Fig. 2a, b**. The remaining 50 patients were assigned to one of two groups based on treatment outcome: those with a clinical response to treatment identified as an FEV1 increase of more than 100 ml and those with an FEV1 increase of less than 100 ml, i. e., those classified as non-responders. The characteristics of the patients in the two groups are summarized in ▶ **Table 1**.

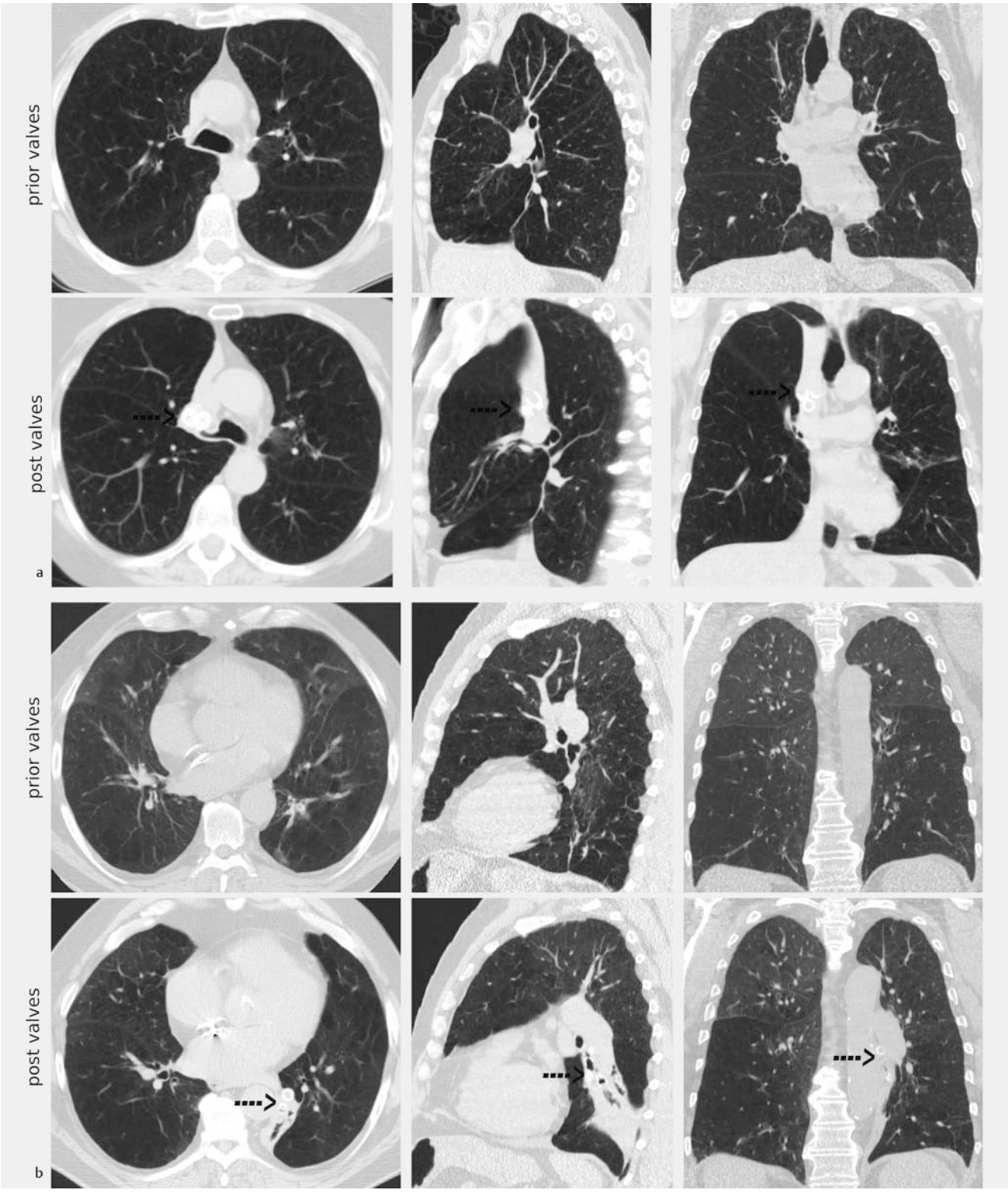
Quantitative computed tomography

Patients scheduled for ELVR underwent computed tomography (CT) for emphysema evaluation and selection of the target lobe before treatment and approximately three months after endoscopic valve implantation for follow-up assessment. All CT scans were acquired with the exact same CT scanner (Light Speed Ultra 8, General Electric Healthcare, Chicago, IL, USA) using the same standardized protocol (slice thickness 1.25 mm, pitch = 1, 120 kVp, 100 mA, kernel "standard"). CTDIvol for these scans was always 3.02 mGy, resulting in a mean DLP of 104.97 mGy*cm



▶ **Fig. 1** Coronal and sagittal 3 D surface views of the lung generated by processing pulmonary CT scans with MeVisPULMO 3 D. The surface views depict the lung lobes in semitransparent colours and voxels with an attenuation below –950 HU, i. e., emphysematous lung parenchyma, in orange/yellow. Quantitative CT parameters for patient **A** with homogeneous emphysema: lung volume: 5634 ml; total lung emphysema score: 25 %; targeted lobe volume (= left upper lobe): 1225 ml; targeted lobe emphysema score: 27 %; interlobar heterogeneity index of the targeted lobe and the ipsilateral non-targeted lobe: 3 %. Quantitative CT parameters for patient **B** with heterogenous emphysema: lung volume: 5597 ml; total lung emphysema score: 24 %; targeted lobe volume (= right upper lobe): 1302 ml; targeted lobe emphysema score: 40 %; interlobar heterogeneity index of the targeted lobe and the ipsilateral non-targeted lobe: 30 %.

▶ **Abb. 1** Coronare and sagittale 3 D Oberflächenansicht der Lunge erstellt aus dem Datensatz der Thorax-CT mit der Software MeVisPULMO 3 D. Voxel mit einer Dichte unter –950 HU, d. h. emphysematöses Lungenparenchym, sind gelborange und die Lungenlappen in verschiedenen halbtransparenten Farben dargestellt. Quantitative CT Parameter von Patient **A** mit homogen verteiltem Lungenemphysem: Gesamtlungenvolumen: 5634 ml; Emphysemindex der gesamten Lunge: 25 %; Ziellappenvolumen (= linker Oberlappen): 1225 ml; Emphysemindex des Ziellappens: 27 %; interlobärer Heterogenitätsindex zwischen Ziellappen und ipsilateralem Nichtziellappen: 3 %. Quantitative CT Parameter von Patient **B** mit heterogen verteiltem Lungenemphysem: Gesamtlungenvolumen: 5597 ml; Emphysemindex der gesamten Lunge: 24 %; Ziellappenvolumen (= rechter Oberlappen): 1302 ml; Emphysemindex des Ziellappens: 40 %; interlobärer Heterogenitätsindex zwischen Ziellappen und ipsilateralem Nichtziellappen: 30 %.



▶ **Fig. 2** **a** Example of a patient with ELVR of the right upper lobe showing axial, sagittal and coronal CT images of the lung before and after valve insertion. The arrows point towards the valves and resulting atelectatic lung lobe. **b** Example of a patient with ELVR of the left lower lobe showing axial, sagittal and coronal CT images of the lung before and after valve insertion. The arrows point towards the valves and resulting atelectatic lung lobe.

▶ **Abb. 2** **a** Beispiel eines Patienten mit ELVR des rechten Oberlappens mit Darstellung der axialen, sagittalen und koronaren CT-Schnittbilder vor und nach Ventilimplantation. Die Pfeile zeigen auf die implantierten Ventile und die resultierende nachgeschaltete Atelektase. **b** Beispiel eines Patienten mit ELVR des linken Unterlappens mit Darstellung der axialen, sagittalen und koronaren CT-Schnittbilder vor und nach Ventilimplantation. Die Pfeile zeigen auf die implantierten Ventile und die resultierende nachgeschaltete Atelektase.

▶ **Table 1** Baseline characteristics of responders and non-responders.

▶ **Tab. 1** Ausgangscharakteristika von Therapieansprechern und Therapieversagern.

parameters	responders ΔFEV1 > 100 ml	non-responders ΔFEV1 < 100 ml	P-value
number	32	18	–
age (years)	66.8 ± 5.6	65.7 ± 7.7	0.762
sex (male/female)	18/14	13/5	–
FEV1 (% pred.)	24.9 ± 6.4	27.8 ± 7.7	0.131
residual volume (% pred.)	222.9 ± 45.3	212.8 ± 37.3	0.442
vital capacity (% pred.)	62.7 ± 15.9	65.0 ± 14.0	0.342
total lung volume (ml)	6760 ± 1423	7067 ± 1186	0.342
targeted lobe volume (ml)	1730 ± 392	1735 ± 439	0.832
total lung emphysema score (%)	32.0 ± 8.1	27.6 ± 8.7	0.120
targeted lobe emphysema score	41.0 ± 11.3	32.3 ± 11.3	0.022
emphysema heterogeneity index[1]	16.5 ± 9.8	7.7 ± 9.4	0.008
targeted lobe (upper lobe/ lower lobe)	15/17	6/12	–

Responders = patients with ΔFEV1 > 100ml; non-responders = patients with ΔFEV1 < 100 ml. Data are presented as mean ± standard deviation. P-values were calculated for continuous variables using the Mann-Whitney U-test. Quantitative computed tomography parameters are highlighted with a grey background. FEV1: forced expiratory volume in 1 second; % pred.: Percent of the predicted value

[1] Interlobar emphysema heterogeneity index = targeted lobe emphysema score – ipsilateral non-targeted lobe emphysema score (disregarding the right middle lobe)

(range: 99.39 – 128.75), dependent on the patient's size and weight.

All scans were obtained in deep inspiration and without intravenous contrast medium. Quantitative analysis of the chest CT scans was performed using the MeVisPULMO 3 D software (v3.42, Fraunhofer MEVIS, Bremen, Germany) with semiautomatic segmentation of the lung into the lung lobes and quantification of emphysematous lung parenchyma using the density mask technique as described in the literature [19, 20]. Full datasets of axial slices without gaps were used for the analysis.

The quantitative parameters derived from the CT scans with this technique included total lung volume, targeted lobe volume, total lung emphysema score and targeted lobe emphysema score. The emphysema score is defined as the ratio of voxels with a density below a certain threshold to the total number of voxels in the region of interest, i. e. the entire lung or a specific lobe. We chose to go by the frequently used attenuation threshold of –950 HU [21 – 23]. The interlobar heterogeneity index was in turn calculated from the emphysema scores of adjacent ipsilateral lung lobes as described in the literature [1, 24] using the following formula: Heterogeneity index = targeted lobe emphysema score – ipsilateral non-targeted lobe emphysema score disregarding the right middle lobe. An example of a qCT analysis of two different lungs and the resulting parameters are presented in ▶ **Fig. 1**.

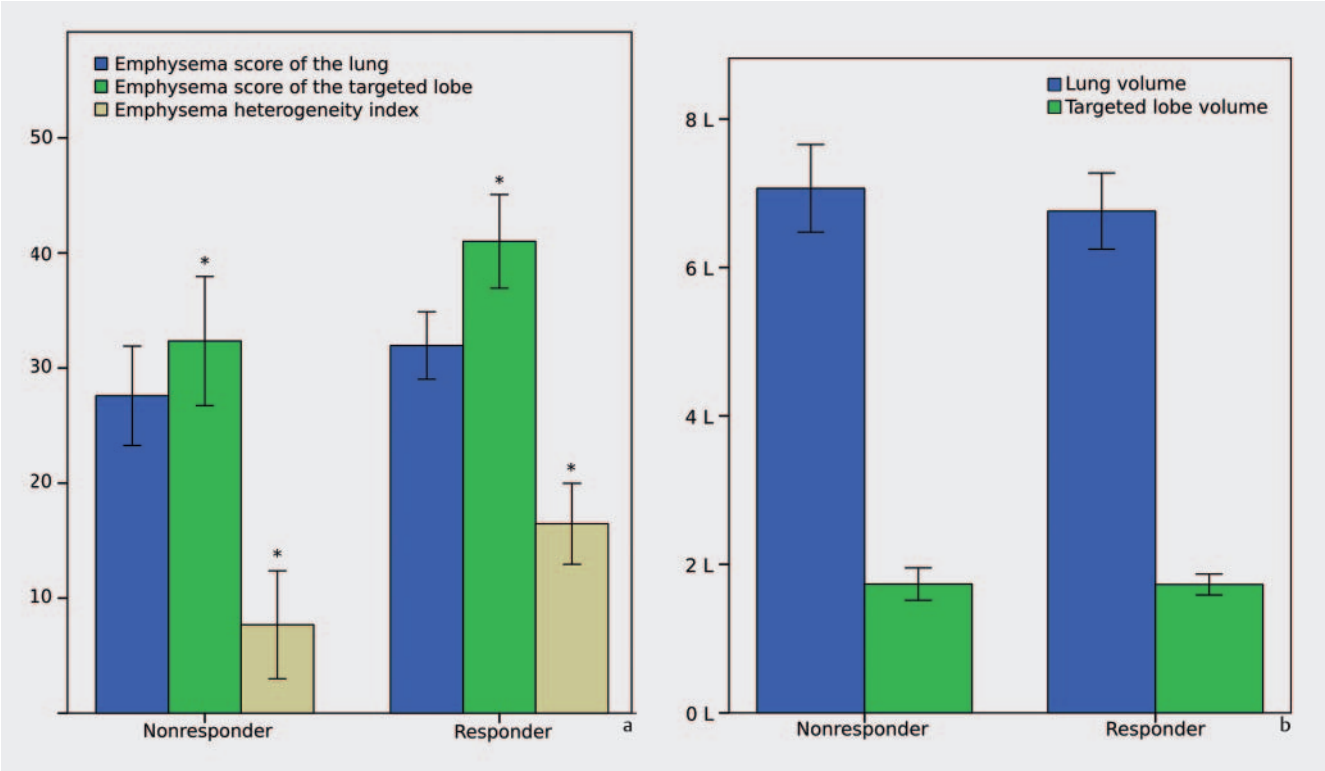
Statistics

For comparisons of parameters between two independent samples, we performed Mann-Whitney U-tests. Furthermore, the influence of qCT parameters on clinical outcome assessed as increase in FEV1 was modeled using logistic regression analysis with stepwise backward variable elimination. A two-tailed p-value < 0.05 was considered statistically significant. The SPSS Statistics 19.0.0 software package (IBM Corporation, Armonk, NY USA) was used for all statistical analyses.

Results

▶ **Table 1** shows the patient characteristics of the two groups, i. e., those with an FEV1 increase of > 100 ml classified as responders to treatment and those with an FEV1 increase < 100 ml classified as non-responders to treatment. The qCT parameters of the two groups, which are the focus of this study, are highlighted with a grey background in ▶ **Table 1** and are additionally visually depicted in ▶ **Fig. 3a, b**. The Mann-Whitney U-tests for two independent samples showed that responders and non-responders did not differ significantly in basic patient characteristics and baseline lung function test findings, thereby ruling out simple confounding issues. Among the qCT parameters investigated in this study, only the interlobar emphysema heterogeneity index (P-value of 0.008) and the total lung emphysema score (P-value of 0.022) showed a statistically significant difference between responders and non-responders in the Mann-Whitney U-test (▶ **Table 1**).

However, in multiple logistic regression analysis with backward selection and FEV1 improvement of more than 100 ml as the



▶ **Fig. 3** **a** Emphysema score of the lung, emphysema score of the targeted lobe and interlobar emphysema heterogeneity index of nonresponders (FEV1 increase < 100 ml after ELVR) versus responders (FEV1 increase > 100 ml after ELVR).* Indicates a statistically significant difference between the two groups in the Mann-Whitney-U-Test. **b** Lung volume and targeted lobe volume of nonresponders (FEV1 increase < 100 ml after ELVR) versus responders (FEV1 increase > 100 ml after ELVR).

▶ **Abb. 3** **a** Emphysemscore der gesamten Lunge, Emphysemscore des Ziellappens und interlobärer Heterogenitätsindex von Therapieversagern (FEV1 Zunahme nach ELVR < 100 ml) versus Therapieansprechern (FEV1 Zunahme nach ELVR > 100 ml).* Kennzeichnet statistisch signifikante Unterschiede im Mann-Whiney-U-Test zwischen den zwei Gruppen. **b** Lungenvolumen und Ziellappenvolumen von Therapieversagern (FEV1 Zunahme nach ELVR < 100 ml) versus Therapieansprechern (FEV1 Zunahme nach ELVR > 100 ml).

dependent variable, only the interlobar emphysema heterogeneity index showed a statistically significant impact on the outcome of ELVR (P-value of 0.008) while targeted lobe volume, lung volume, total lung emphysema score and targeted lobe emphysema score did not (P-value > 0.05) (▶ **Table 2**).

Discussion

Our study suggests that, of all qCT parameters commonly obtained prior to endoscopic lung volume reduction, only the interlobar emphysema heterogeneity index and possibly, to a lesser extent, the total lung emphysema score can identify patients likely to respond to ELVR in terms of FEV1 improvement. With respect to the interlobar emphysema heterogeneity index, our results are in accordance with various previous studies [1, 12, 14, 16, 25]. It is a surprising result of our study, which to our knowledge has not been shown before, that, contrary to expectation, the total lung emphysema score does not predict outcome of ELVR. For the targeted lobe emphysema score, our results are less straightforward as the parameter showed a statistically significant difference between responders and non-responders in the Mann-Whitney U-test but not in multiple logistic regression analysis with stepwise backward elimination. Our interpretation is that the targeted lobe emphysema heterogeneity has a negligible impact on outcome when the heterogeneity index is already taken into account in patient and lobe selection. It needs to be emphasized, though, that these results were obtained in a preselected patient population, i. e., all treated patients had advanced COPD (GOLD Stage 3 or 4) with extensive emphysema of the lung and the targeted lobe (see ▶ **Table 1**). The results may therefore not apply to patients with minor emphysema. Results for lung volume and targeted lobe volume have not been reported before either, to our knowledge. However, our results for these parameters are not very surprising as normal lung volumes vary greatly between individuals. Increased lung volumes due to overinflation in the context of pulmonary emphysema can probably only be identified intraindividually, i. e., by comparing the lung volume of a fully grown patient before the onset of pulmonary emphysema with the lung volume of the same patient at the time of disease manifestation. Such data were not available in this retrospective analysis. Another issue to be mentioned is the uneven distribution of upper versus lower lobe treatment in the two groups analyzed in our study. The percentage of upper lobe treatments was smaller in the group of responders compared to the group of non-responders. As upper

▶ **Table 2** Multiple logistic regression analysis with backward selection.

▶ **Tab. 2** Multivariable Regressionsanalyse mit Rückwärtsselektion.

predictors in the regression analysis	P-value	odds	CI 95 %
lung volume	0.873	–	–
targeted lobe volume	0.566	–	–
total lung emphysema score	0.862	–	–
targeted lobe emphysema score	0.508	–	–
Interlobar emphysema heterogeneity index[1]	0.008	1.1	1.0 – 1.2

Dependent variable: ΔFEV1 > 100 ml

[1] Interlobar emphysema heterogeneity index = targeted lobe emphysema score – ipsilateral non-targeted lobe emphysema score (disregarding the right middle lobe)

lobe treatment is sometimes said to yield better outcome than lower lobe treatment [26], this is a possible confounder which cannot be eliminated in this retrospective analysis.

When speaking about "quantitative computed tomography parameters that matter" in the context of selecting patients for endoscopic lobar lung volume reduction with one-way endobronchial valves, computed tomography fissure analysis needs to be mentioned for the sake of completeness which has shown promising results and might help to avoid the bronchoscopy-based Chartis measurements in some cases [27, 28]. In our study population, the absence of collateral ventilation was determined by the Chartis system in all patients and quantitative CT interlobar fissure completeness scores were therefore not evaluated.

Limitations of the study

The small population size and the retrospective design are major limitations of this study, as already discussed above. Our findings are therefore preliminary, and a study in a larger number of patients and preferably a prospective design is needed to validate these results. Furthermore, we used FEV1 as an outcome parameter, while neglecting other important outcome parameters such as change in 6-minute walking test or quality of life (e. g. assessed with a questionnaire). While FEV1 might not capture all aspects of the disease, it is widely recognized as an important outcome parameter [29, 30].

Conclusion

In the treatment of patients with established advanced COPD, the heterogeneity index is the only qCT parameter that predicts the outcome of ELVR. When the heterogeneity index is taken into account, there seems to be no additional benefit of the targeted lobe emphysema score in terms of predicting outcome. Other commonly used parameters such as total lung emphysema score, lung volume and targeted lobe volume do not have an impact on the outcome of ELVR and therefore need not be considered when assessing patients with advanced COPD for ELVR.

Conflict of Interest

The authors declare that they have no conflict of interest.

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