

Interventional therapy in patients with severe emphysema: evaluation of contraindications and their incidence

Markus Polke , Matthias Rötting, Nilab Sarmand, Johannes Krisam, Ralf Eberhardt, Felix J.F. Herth and Daniela Gompelmann

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Abstract

Background: Endoscopic and surgical interventions may be beneficial for selected patients with emphysema. Rates of treatment failure decrease when the predictors for successful therapy are known. The aim of the study was to evaluate the number of patients with severe emphysema who were not eligible for any intervention, and the reasons for their exclusion.

Methods: The study was a retrospective analysis of 231 consecutive patients with advanced emphysema who were considered for interventional therapy in 2016 at the Thoraxklinik, Heidelberg, Germany. The reasons for not receiving valve or coil therapy were assessed for all patients who did not receive any therapy.

Results: Of the 231 patients, 50% received an interventional therapy for lung volume reduction (LVR) (82% valve therapy, 6% coil therapy, 4.3% polymeric LVR or bronchial thermal vapour ablation, 4.3% total lung denervation, and 3.4% lung volume reduction surgery [LVRS]). A total of 115 patients did not undergo LVR. Out of these, valve or coil therapy was not performed due to one or more of the following reasons: incomplete fissure in 37% and 0%; missing target lobe in 31% and 30%; personal decision in 18% and 28%; pulmonary function test results in 8% and 15%; ventilatory failure in 4% and 4%; missing optimal standard medical care and/or continued nicotine abuse in 4% and 3%; general condition too good in less than 1% and 3%; cardiovascular comorbidities in 0% and 3%; age of patient in 0% and less than 1%. Both techniques were not performed due to one or more of the following reasons: solitary pulmonary nodule(s)/consolidation in 27%; bronchopathy in 7%; neoplasia in 2%; destroyed lung in 2%; prior LVRS in less than 1%.

Conclusions: The main reason for not placing valves was an incomplete fissure and for coils a missing target lobe. Numerous additional contraindications that may exclude a patient from interventional emphysema therapy should be respected.

Keywords: chronic obstructive pulmonary disease, emphysema, endoscopic lung volume reduction

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Introduction

Endoscopic and surgical lung volume reduction (LVR) may be beneficial to patients with chronic obstructive pulmonary disease (COPD) and severe emphysema. Lung volume reduction surgery (LVRS) that minimizes hyperinflation leads to improvement of lung function, exercise capacity and quality of life and is associated

with survival benefit in patients with upper lobe-predominant emphysema.¹ However, LVRS carries significant risk for morbidity and mortality and thus has stimulated the search for alternative, minimally invasive therapeutic approaches. Endoscopic lung volume reduction (ELVR) aims at LVR with less attendant risk. Endoscopic valve therapy, the best studied

Correspondence to:
M. Polke
Pneumology and
Critical Care Medicine,
Thoraxklinik at University
of Heidelberg, Röntgenstr.
1, 69126 Heidelberg,
Germany
markus.polke@med.uni-heidelberg.de

M. Rötting
N. Sarmand
Pneumology and
Critical Care Medicine,
Thoraxklinik at University
of Heidelberg, Heidelberg,
Germany

J. Krisam
Institute of Medical
Biometry and Informatics,
University of Heidelberg,
Heidelberg, Germany

R. Eberhardt
F.J.F. Herth
D. Gompelmann
Pneumology and
Critical Care Medicine,
Thoraxklinik at
University of Heidelberg,
Heidelberg, Germany,
and Translational
Lung Research Center
Heidelberg (TLRCH,
German Center for Lung
Research), Heidelberg,
Germany

technique, results in a lobar atelectasis of the emphysematous lung lobe and thus improves symptoms and long-term outcome.^{2,3} Coil therapy accomplishes volume reduction by torquing the bronchi.^{4,5} Bronchoscopic thermal vapour ablation (BTVA) results in LVR by the instillation of heated water vapour leading to a local inflammatory reaction and thus to a lung volume scar and fibrosis after some weeks.^{6,7} In polymeric lung volume reduction (PLVR), which is very similar to BTVA, a polymer sealant is used instead of water vapour to induce a local inflammatory reaction.⁸ Besides ELVR techniques, targeted lung denervation (TLD) presents another endoscopic therapeutic option for patients with advanced COPD. TLD, which so far has only been used in clinical trials, focuses on persistent bronchodilation. The parasympathetic innervation of the lungs is ablated leading to a decrease in airway obstruction, smooth muscle tone and mucous production.⁹

LVRS, ELVR or TLD are considered for patients with advanced COPD and emphysema who still have symptoms and significant impaired lung function despite optimal pharmacological therapy and rehabilitation. Although the LVRS and ELVR approaches aim at hyperinflation reduction, they are different in their mechanism of action, dependence for interlobar collateral ventilation (CV), reversibility and spectrum of complications. Thus, valve therapy is the only reversible technique and also the only technique where an absent interlobar CV is a prerequisite for successful outcome. An expert panel recommendation on ELVR presented an algorithm that assists in patient selection for the different available LVR techniques. Different diagnostic methods and requirements for successful interventions have been described.¹⁰ Although the exclusion criteria for the various therapeutic approaches are known, there are no data on their prevalence and impact on excluding patients from treatment in clinical practice. Furthermore, even though ELVR is a useful method in patients with severe emphysema, there has been criticism on the insufficient and uncritical selection of patients leading to an unsuccessful procedure.¹¹ Therefore, the aim of this work was to evaluate the actual number of patients eligible for any intervention in a screening cohort of patients with COPD and severe emphysema and to describe the prevalence of exclusion criteria and their impact on patient selection.

Methods

In this retrospective analysis, the database compiled by the authors was queried for all patients with advanced emphysema who underwent screening examinations for ELVR in 2016 at the Thoraxklinik, University of Heidelberg, Germany. All patients gave general consent for the scientific use of the data acquired during hospitalization. The local ethics committee of Heidelberg approved the protocol of this trial (S-202/2017).

Subjects and LVR evaluation

Patients enrolled in this analysis underwent lung function testing, laboratory testing, blood gas analysis, exercise tests, multidetector computed tomography (MDCT) of the chest and bronchoscopy as needed. The laboratory testing included cell counts, clinical biochemistry (i.e. electrolytes, liver and kidney function, inflammation markers, alpha 1-antitrypsin) and coagulation. CV was assessed by MDCT fissure analysis that was performed visually by the radiologists and in borderline results supplemented by Chartis® measurement.¹² For evaluation of emphysema distribution and for identifying the target lobe, a software-based analysis (YACTA [yet another CT analyser]) was performed in each patient calculating the lobar volumes and lobar emphysema index.¹³

According to the expert panel recommendation,¹⁰ the first step is to assess the fissure integrity as surrogate for CV. In patients with absent CV, reversible valve treatment is considered as the treatment of choice. In patients with significant CV, the alternative, irreversible LVR techniques or TLD are considered but were offered mostly within clinical trials.

Study design and data collection

An assessment was made of how many patients of the analysed cohort received a method of LVR, and the chosen LVR method identified. Furthermore, exclusion criteria for the patients who did not receive valve or coil therapy were assessed. The different reasons for not receiving valve or coil implantation were collected from the baseline data and discharge letter. The frequency of each exclusion criterion in the cohort was assessed. While valve therapy, coil therapy and LVRS presented an available procedure outside clinical trials, BTVA and PLVR were only performed within clinical trials.

Statistical analysis

Statistical analysis was performed by means of tabulating mean \pm standard deviation for continuous parameters, while absolute and relative frequencies were used to describe categorical parameters. This was performed for the total patient population and separately with regard to intervention status. Continuous parameters were compared between the intervention group and the nonintervention group using two-sample *t* tests. Statistical tests were performed as part of an exploratory data analysis and are thus not adjusted for multiple testing. *p* values smaller than 0.05 were regarded as statistically significant. All analyses were performed using R version 3.4.3 (<http://r-project.org>).

Results

Overall, 231 patients with COPD (men 59%, mean age 64.0 years \pm 7.8 years) received baseline examinations for a possible interventional therapy to reduce lung volume in 2016 at the Thoraxklinik, University of Heidelberg. Baseline characteristics are presented in the Table 1.

LVR evaluation

Out of the 231 patients, 50.2% (116/231) received a method of LVR whereas 49.8% (115/231) were excluded from LVR therapy. Baseline characteristics between both the intervention group and the nonintervention group were significantly different in residual volume (RV) ($p = *0.009$), total lung capacity (TLC) ($p = *0.002$) and transfer factor for carbon monoxide, adjusted for alveolar volume ($p = *0.006$) (Table 1).

Valve implantation was applied in 82% of patients (96/116), coil therapy in 6% (7/116), PLVR or BTVA in 4% (5/116), TLD in 4% (5/116) and LVRS in 3% (4/116). One of the patients initially received valve implantation, followed by LVRS after valve removal.

A CT fissure analysis was performed for each patient to evaluate the presence of interlobar CV. Depending on the fissure integrity, a Chartis® measurement was added for increased diagnostic yield; in this patient cohort, only 5% of patients received an additional Chartis® measurement. In all other cases, CT fissure analysis seemed to be sufficient to exclude significant interlobar CV.

Reasons for exclusion from valve therapy

The reasons for not receiving valve therapy were analysed in patients who did not undergo any kind of interventional therapy ($n = 115$). There was more than one exclusion criterion in some of the patients.

The following reasons for not receiving valve therapy were identified: incomplete fissure in 37% (43/115), missing target lobe in 30% (31/115), solitary pulmonary nodule(s)/consolidation in 27% (30/115), personal decision in 18% (21/115), pulmonary function test results in 8% (9/115; forced expiratory volume in 1 s (FEV₁) > 40% and/or RV < 165%), bronchopathy in 7% (8/115), ventilatory failure in 4% (5/115), missing optimal standard medical care and/or continued nicotine abuse in 3% (3/115), neoplasia in 2% (2/115), destroyed lung in 2% (2/115), prior LVRS in less than 1% (1/115) or general condition too good in less than 1% (1/115) (see Figure 1). If missing target lobe was a reason for not receiving a therapy, it was due to intralobar heterogeneity in 13 patients, homogeneous emphysema in 4 patients and too little emphysema in 16 patients. The main reason for refusing valve implantation by the patient was the fear of complications.

Reasons for exclusion from coil therapy

The following reasons for not receiving coil implantation were identified, and are listed according to their frequency: personal decision in 28% (32/115), missing target lobe in 26% (30/115), solitary pulmonary nodule(s)/consolidation in 26% (30/115), pulmonary function test results in 15% (17/115; FEV₁ > 45%, FEV₁ < 20% and/or RV < 225%), bronchopathy in 7% (8/115), ventilatory failure in 4% (5/115), general condition too good in 3% (4/115), cardiovascular comorbidities in 3% (4/115), in missing optimal standard medical care and/or continued nicotine abuse in 3% (4/115), neoplasia in 2% (2/115), destroyed lung in 2% (2/115), prior LVRS in less than 1% (1/115) or the age of the patient in less than 1% (1/115) (see Figure 2). The main reason for refusing coil implantation was the fear of complications.

Discussion

There are different interventional therapeutic strategies for patients with severe emphysema.^{11,14} However, only a subgroup of patients with COPD

Table 1. Baseline characteristics of patients who were evaluated for lung volume reduction.

	Intervention group (n = 116)	Nonintervention group (n = 115)	p value
Age			0.017*
<i>N</i>	116	115	
Mean ± SD	65.20 ± 7.09	62.77 ± 8.22	
Median (min; max)	66 (48.0; 79.0)	64 (38.0; 84.0)	
Gender			0.469
Male female	71 (61.2%) 45 (38.8%)	65 (56.5%) 50 (43.5%)	
VC (L)			0.281
<i>N</i>	116	115	
Mean ± SD	2.53 ± 0.85	2.41 ± 0.85	
Median (min; max)	2.4 (0.8; 5.5)	2.4 (0.7; 4.9)	
VC (%)			0.475
<i>N</i>	116	115	
Mean ± SD	70.76 ± 18.98	68.94 ± 19.73	
Median (min; max)	69.2 (30.3; 130.8)	66.7 (28.5; 127.0)	
FEV1 (L)			0.372
<i>N</i>	116	115	
Mean ± SD	0.89 ± 0.30	1.15 ± 3.16	
Median (min; max)	0.9 (0.3; 2.0)	0.8 (0.3; 34.6)	
FEV1 (%)			0.743
<i>N</i>	116	115	
Mean ± SD	32.58 ± 9.88	32.14 ± 10.42	
Median (min; max)	31.6 (15.7; 65.2)	31.1 (11.0; 68.9)	
RV (L)			0.009**
<i>N</i>	114	114	
Mean ± SD	5.85 ± 1.34	5.37 ± 1.38	
Median (min; max)	5.6 (3.5; 9.7)	5.3 (2.3; 9.8)	
RV (%)			0.135
<i>N</i>	114	114	
Mean ± SD	258.23 ± 55.23	246.39 ± 63.69	

(Continued)

Table 1. (Continued)

	Intervention group (<i>n</i> = 116)	Nonintervention group (<i>n</i> = 115)	<i>p</i> value
Median (min; max)	247.6 (148.6; 474.9)	234.25 (94.9; 466.5)	
TLC (L)			0.002**
<i>N</i>	116	114	
Mean ± SD	8.45 ± 1.64	7.79 ± 1.51	
Median (min; max)	8.3 (5.1; 13.3)	7.8 (3.7; 11.8)	
TLC (%)			0.032*
<i>N</i>	116	114	
Mean ± SD	139.86 ± 19.51	133.07 ± 27.57	
Median (min; max)	136.75 (105.8; 219.4)	134.1 (11.6; 237.5)	
TLCO/SB (%)			0.056
<i>N</i>	101	94	
Mean ± SD	29.83 ± 13.05	33.68 ± 14.87	
Median (min; max)	27.4 (5.2; 67.2)	31.1 (1.8; 73.8)	
TLCO/VA (%)			0.006**
<i>N</i>	104	94	
Mean ± SD	41.92 ± 17.59	49.72 ± 22.07	
Median (min; max)	40.1 (11.6; 112.6)	47.2 (11.7; 118.3)	

p values based on chi-square test for gender, and on independent samples *t* test for all other variables (**p* < 0.05; ***p* < 0.01). FEV1, forced expiratory volume in 1 s; RV, residual volume; SD, standard deviation; TLC, total lung capacity; TLCO/SB, transfer factor for carbon monoxide, single breath; TLCO/VA, transfer factor for carbon monoxide, adjusted for alveolar volume; VC, vital capacity.

will benefit from these therapeutic approaches, which may also be associated with risks, so that patient selection is crucial.

Based on the currently available data, different predictors are known for a successful outcome following the various interventions. It is well known that endoscopic valve therapy only results in clinically relevant benefits in patients with absent interlobular CV. In the latest RCTs (randomized controlled trial), in which only patients with absent CV were enrolled (e.g. STELVIO, BeLieVeR-HIFI, IMPACT, TRANSFORM and LIBERATE), a significant and clinically relevant improvement in lung function, physical capacity and quality of life after valve implantation was

observed.^{3,15–18} Therefore, an absent CV is one of the most important prerequisites for successful valve placement. Besides CV, a high emphysema index of the target lobe to the target lung, a high RV, a low vital capacity and low 6-min walk test have been shown to be predictors for a good outcome following valve therapy.¹⁹ The data for coil therapy including three RCTs are still very limited.^{4,8,19} In the latest RCT, RENEW, coil implantation showed a statistically significant improvement in lung function, physical capacity and quality of life but of uncertain clinical importance.⁵ Thereby, patients with heterogeneous emphysema and a RV of 225% or more exhibited superior response to bilateral coil implantation. For BTVA and PLVR, results from only one RCT

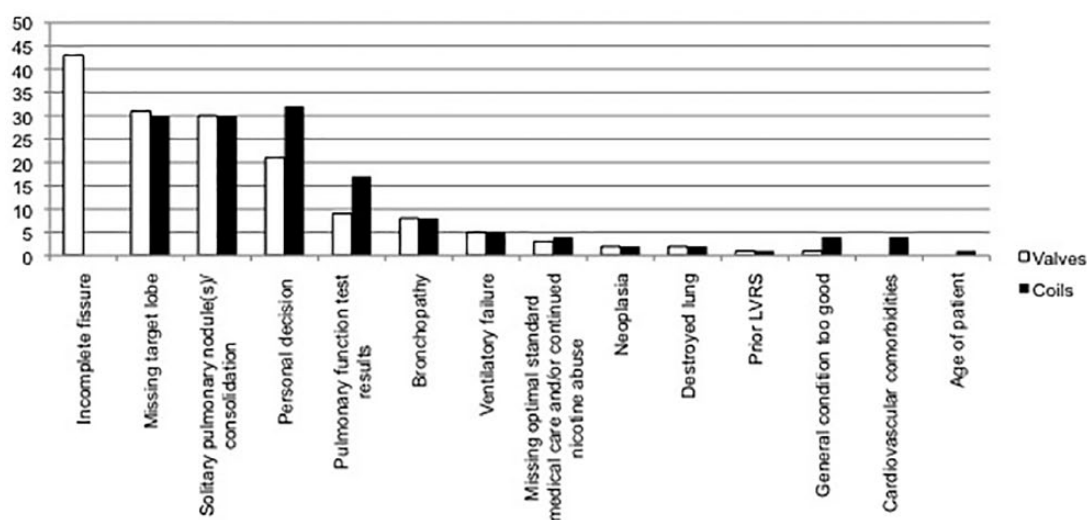


Figure 1. Number of patients with reasons for not receiving valve/coil therapy. LVRS, lung volume reduction surgery.

have been published demonstrating a beneficial outcome in patients with upper lobe-predominant emphysema.⁷ As these techniques induce an inflammatory reaction, special attention has to be given to respiratory adverse events and only patients with a FEV₁ of more than 20% and transfer factor for carbon monoxide, single breath of more than 20% should be treated because of safety aspects. PLVR in particular is associated with a high-risk profile so that the use of this technique is limited. Due to lack of sufficient data, BTVA, PLVR and also TLD should only be used within clinical trials, when alternative ‘established’ methods are not indicated.

Besides endoscopic approaches, LVRS is also a method to reduce lung volume that may be beneficial in a selected patient cohort. However, the National Emphysema Treatment Trial (NETT) showed that patients with low FEV₁ and either homogeneous emphysema or very low carbon monoxide diffusing capacity have a high risk of death after LVRS.²⁰ This demonstrates the importance of accurate patient selection prior to any intervention.

The present patient cohort was examined for any interventional therapy at the University of Heidelberg in 2016. Over this time period, valves, coils and LVRS were performed within or outside clinical trials, whereas PLVR, BTVA and TLD were only performed within clinical studies or registry-based studies. As patient enrolment in clinical

trials is strictly regulated, the difference in availability of the various techniques certainly contributed to the choice of interventional technique.

The results of these trials enhance the importance of precise patient selection as not every patient will benefit from LVR therapy. An expert panel recommendation for ELVR describes the different criteria for suitable patients,¹⁰ but so far it is not known how many patients are excluded from these therapeutic approaches in clinical practice. As the ELVR techniques are mostly straightforward technical methods, one legitimate concern is their uncritical use. Therefore, it is of great importance to emphasize the various contraindications and their impact on patient selection.¹¹ The data from this current analysis showed that only half of the patients who initially underwent examination for ELVR evaluation eventually received therapy. One important finding is that patients who received any LVR technique had a significantly higher mean hyperinflation measured by RV and TLC compared with patients who were not candidates for these therapeutic approaches. This result resembles previous findings that patients with more severe hyperinflation will more likely exhibit superior response to treatment. The most common reason for not receiving valve therapy was incomplete fissures that present a surrogate for CV and thus indicate unsuccessful valve therapy. Another contraindication for valve or coil therapy was a missing target lobe. Although valves and coils can be used effectively in patients with heterogeneous and

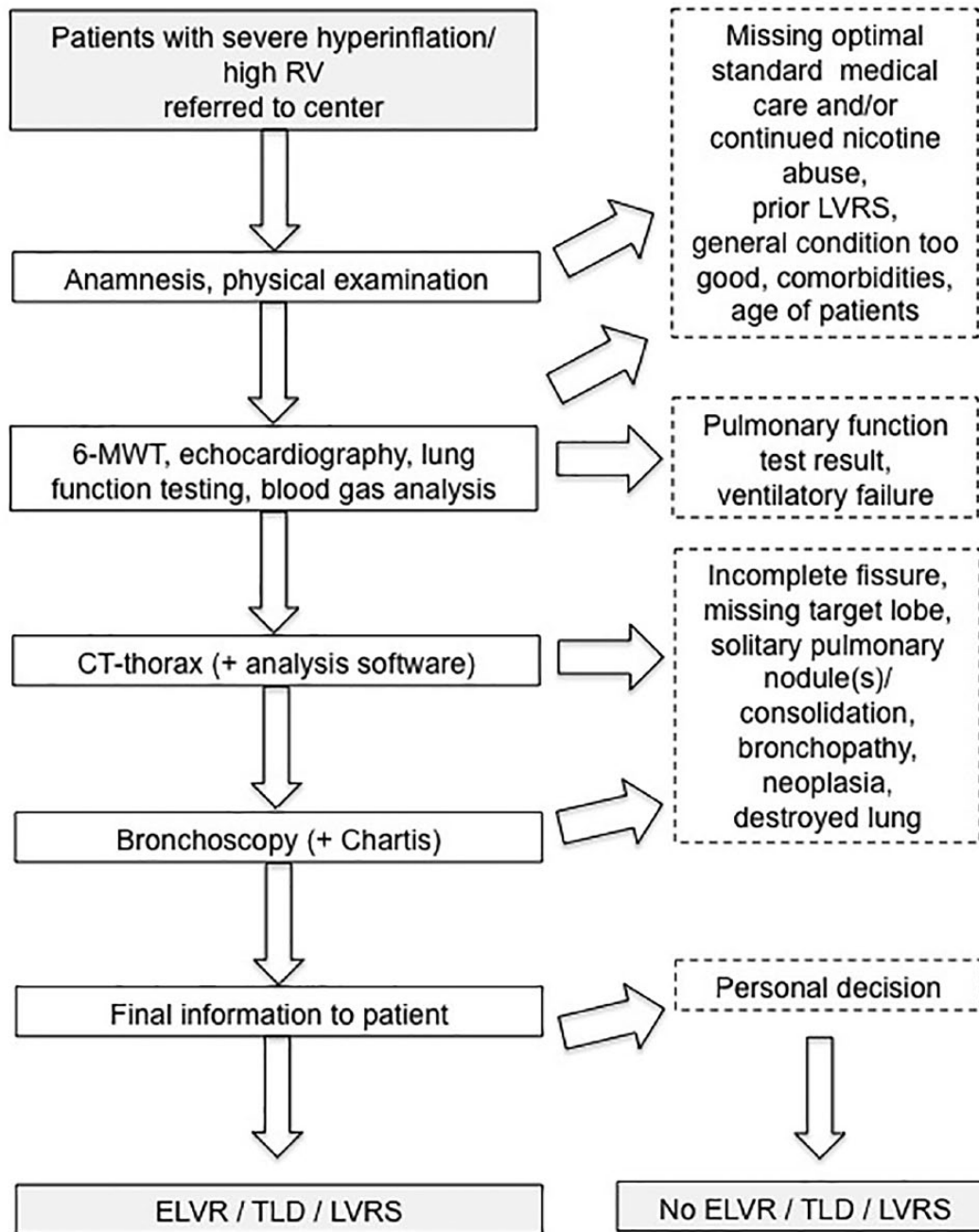


Figure 2. A flowchart showing patient exclusion from ELVR/TLD/LVRS. 6-MWT; 6-min walk test; CT, computed tomography; ELVR, endoscopic lung volume reduction; LVRS, lung volume reduction surgery; RV, residual volume; TLD, targeted lung denervation.

homogeneous emphysema, a high proportion of patients with emphysema are affected not only by interlobar but also by intralobar heterogeneity so that valves or coils that target the entire lobe are not an adequate treatment.²¹ Further reasons were solitary pulmonary nodule(s)/consolidation. In these patients, different strategies are pursued

depending on the location of the pulmonary nodule. Patients with a pulmonary lesion in the target lobe should be excluded from immediate valve therapy, as MDCT follow up of the nodule would not be possible due to the valve-induced lobar atelectasis. A follow-up MDCT scan may be helpful in assessing probability of malignancy. In the case

of a suspicious nodule, lobectomy by LVRS and simultaneous histological diagnosis of the nodule should be discussed. If the pulmonary lesion is found in another lung lobe than the target lobe, ELVR can be performed immediately according to the actual guidelines or the intervention can be postponed based on an individual decision.²² Another important contraindication is the personal decision of the patient. It is crucial to discuss the individual benefit–risk profile with the patient and to support the patient’s decision. In addition, pulmonary function test results were another reason why some patients did not receive valve implantation.

These findings strengthen the conclusion that only a selected group of patients are optimal candidates for ELVR or LVRS. This analysis summarizes the possible contraindications and their incidence. As precise patient selection is crucial for successful outcomes following intervention, patients who exhibit these contraindications should be excluded from these therapeutic options. As patients’ expectations are often very high, patients should be informed prior to evaluation for an interventional therapy, that only a selected group of patients will benefit from ELVR or LVRS and that they may be rejected from an interventional therapy.

It is known that endoscopic/surgical interventions can only be beneficial for selected patients with emphysema. Knowing the predictors for successful therapy means treatment failure can be prevented. Therefore, a precise and strict selection of patients is necessary. Not every patient suffering under severe emphysema is a candidate for intervention. If a specific method is performed in correctly selected patients, the interventional therapy will be successfully established in patients with severe emphysema. Therefore, one sign for precise patient selection at a specialized centre where LVR is performed could be the rate of patients receiving LVR out of a baseline cohort. Obviously, the number of patients and the results have to be considered as well but it shows a critical choice of patients.

One limitation of the current analysis is that the presented data came from only one specialized centre. Data from other centres have to be considered as well. Furthermore, it must be kept in mind, that the enrolled patients reflect a ‘preselected’ cohort of patients with advanced emphysema. In the majority of subjects, the required

lung function thresholds for LVR were fulfilled according to current LVR recommendations, as these patients were referred to the hospital for LVR evaluation by pneumologists. Requirements for patients being referred to the centre in Heidelberg for ELVR were lung function test results proving severe hyperinflation. Further diagnostic tests, namely CT of the thorax and, if necessary, bronchoscopy with Chartis® measurement, were performed in the centre (Figure 2).

A discussion in the context of a multidisciplinary team is important and recommended to determine the best LVR method for patients with severe emphysema.¹⁰ Each individual patient has to be discussed by pneumologists, radiologists and thoracic surgeons. Interdisciplinary LVR boards might be helpful in finding the best therapy for a patient.

In conclusion, patient selection is important and obligatory for a successful intervention. Not only inclusion criteria but also exclusion criteria might help physicians in this matter. The quality of a specialized centre will depend on the selection of patients.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

ORCID iD

Markus Polke  <https://orcid.org/0000-0002-9498-7066>

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