

Emphysema: Imaging for Endoscopic Lung Volume Reduction

Lungenemphysem: Bildgebung bei endoskopischer Lungenvolumenreduktion

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Key words

- emphysema
- thoracic imaging
- endoscopic lung volume reduction

Abstract

Chronic obstructive pulmonary disease (COPD) is characterized by two entities, the more airway-predominant type (“bronchitis”) on the one hand, and emphysema-predominant type on the other. Imaging via high-resolution computed tomography plays an important role in phenotyping COPD. For patients with advanced lung emphysema, new endoscopic lung volume reduction therapies (ELVR) have been developed. Proper selection of suitable patients requires thin-section reconstruction of volumetric CT image data sets also in coronal and sagittal orientation are required. In the current manuscript we will describe emphysema subtypes (centrilobular, paraseptal, panlobular), options for quantifying emphysema and this importance of regional distribution (homogeneous or heterogeneous, target area) as this is crucial for patient selection. Analysis of the interlobular fissures is obligatory despite the lack of standardization, as incomplete fissures indicate collateral ventilation (CV) via parenchymal bridges, which is an important criterion in choosing endoscopic methods of LVR. Every radiologist should be familiar with modern LVR therapies such as valves and coils, and furthermore should know what a lung doctor expects from radiologic evaluation (before and after ELVR). Finally we present a checklist as a quick reference for all steps concerning imaging for ELVR.

Key points:

- ▶ High-resolution computed tomography with 3 D reconstructions becomes increasingly important in phenotyping COPD and diagnosing emphysema.
- ▶ Patient selection is crucial for modern techniques of lung volume reduction, such as valves or coils.

- ▶ Radiology plays a key role for fissural analysis and identifying a target area.
- ▶ Success of this therapy depends on experience and multidisciplinary cooperation.

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Zusammenfassung

Die Chronisch Obstruktive Lungenerkrankung (COPD) ist eine Erkrankung mit zwei verschiedenen Ausprägungsarten, dem eher atemwegdominierten Typ („Bronchitis“) und dem emphysemdominierten Typ. Für die Phänotypisierung spielt die Bildgebung mittels hochauflösender Computertomografie eine wichtige Rolle. Im Falle eines fortgeschrittenen Emphysems bestehen neue zielgerichtete endoskopische Verfahren zur Lungenvolumenreduktion (ELVR). Zur Prüfung der Indikation ist die Erhebung von Volumendatensätzen nötig, die dünne Rekonstruktionen auch in koronarer und sagittaler Schnittführung ermöglichen. Im Folgenden werden neben der Differenzierung zwischen den verschiedenen Emphysemarten (zentrilobulär, panlobulär, paraseptal) auch die Möglichkeiten der Quantifizierung und die Bedeutung der regionalen Emphysemverteilung (homogen oder heterogen, Zielareal) für die Patientenselektion erläutert. Die Analyse der interlobären Fissuren ist trotz bislang fehlender Standardisierung obligat, da bei inkompletten Fissuren von einer Kollateralventilation (CV) über Parenchymbrücken auszugehen ist, einem wichtigen Kriterium für die Auswahl des Verfahrens. Jeder Radiologe sollte die modernen Verfahren der LVR wie Ventile oder Coils kennen und wissen, welche radiologischen Informationen der Pneumologe vor und

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Bibliography

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nach der Anwendung der ELVR benötigt. Dazu wurde zusammenfassend eine Checkliste für die radiologische Emphysem-diagnostik erstellt.

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most common diseases worldwide, having a prevalence of approximately 9% in Germany [1]. The disease is diagnosed according to clinical and functional findings, and classified by severity (GOLD stage 1–4) and into groups according to GOLD guidelines [2].

Even patients with similar degrees of impaired pulmonary function yield completely different morphological pictures through radiological imaging, both in terms of the extent ("quantifying") and the prevailing type of morphological changes ("qualifying"). Distinctions must be made between emphysema- and airway-predominant "phenotype", with classification being made with the aid of computed tomography [3–6]. Imaging diagnostics have become increasingly relevant in recent years, since different strategies exist for the two patient groups which open new perspectives particularly for the emphysema group.

Modern emphysema therapy includes, above all, endoscopic lung volume reduction methods (ELVR). In particular, valves and coils are seeing increased use, thus requiring radiologists to become familiar with the different methods and diagnostic criteria.

Phenotyping COPD: Emphysema?

The severity and course of COPD is determined by gathering the patient's history and testing lung function. Important parameters are forced exhalation (FEV₁, forced expiratory volume in one second), FEV₁/FVC quotient (Tiffeneau index) and diffusion capacity. The ITGV (intrathoracic gas volume) with RV (residual volume) and TLC (total lung capacity) are used to detect hyperinflation. To ascertain their normal routine physical capacity, patients undergo a standardized 6-minute walking test.

Severity staging according to GOLD is founded on the FEV₁ limitation based on values following bronchodilation (GOLD 1 FEV₁ ≥ 80%, GOLD 2 FEV₁ < 80% ≥ 50%, GOLD 3 FEV₁ < 50% ≥ 30%, GOLD 4 < 30% of target). Patients are additionally classified into groups A through D according to symp-

toms and exacerbations per year. However, the morphological information indicating whether emphysema is present and, if so, to what extent and how it is distributed can be obtained only through medical imaging. According to the EvA study, it is possible to classify cases as E- (emphysema) or A- (airway disease) type by measuring lung density and bronchial wall thickness [7], most cases being a mixed picture with varying degrees of both components.

Airway type

The chronic inflammatory process reshapes the major and minor airways.

The bronchial walls become thicker (chronic bronchitis) and either narrow (obstruction) or widen (bronchiectasis), while the airways become unstable.

When the minor airways are involved (small airway disease), indirect and direct signs of bronchiolitis are present. In the case of inflammatory (exudative, intraluminal) bronchiolitis with thickening of the bronchiolar wall and displacement of the lumen by secretion, centrilobular, micronodular densifications, which have the appearance of buds on a branch (Tree-in-bud phenomenon) appear as direct signs. With constructive, obliterative bronchiolitis, the minor airways are obstructed, the lumen of the bronchioles collapse upon expiration and air can no longer be expelled (air trapping). This is more clearly visible on expiration images when mosaic-like hypodense areas with trapped air remain (indirect sign), while normally the density increases in healthy lung parenchyma during exhalation. Comparison of inspiratory and expiratory images additionally provides information on the stability of the tracheobronchial system.

Emphysema type

Emphysema is a morphological-structural diagnosis defined as irreversible expansion of the air spaces distal to the terminal bronchioles with destruction of the walls of the affected alveoli, but without any scarring (◉ Fig. 1). Lung performance declines as a result of a loss of gas exchange surface as well as a progressive hyperinflation. LVR measures can be used only for patients suffering from an advanced stage (GOLD III through IV) depending on the type, extent and distribution of their emphysema. It is therefore necessary to first address the classification and subtypes of emphysema.

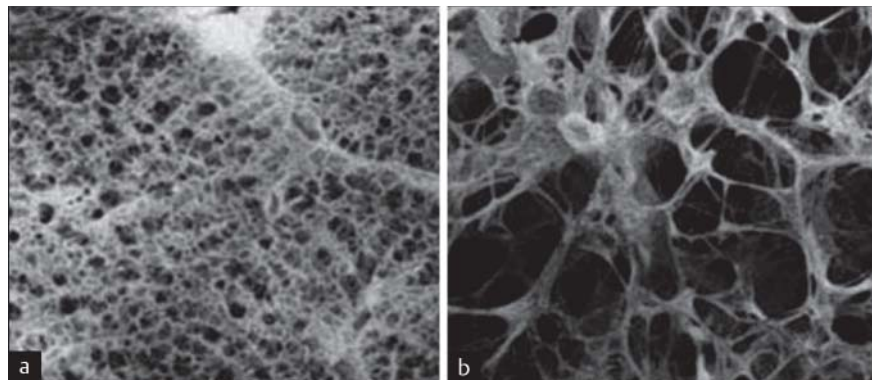


Fig. 1 Healthy **a** and abnormal **b** alveoli on an electron microscopic image. Emphysema (on the right) leads to irreversible destruction of the alveolar walls, which results in a reduced area for gas exchange. (Courtesy of PulmonX).

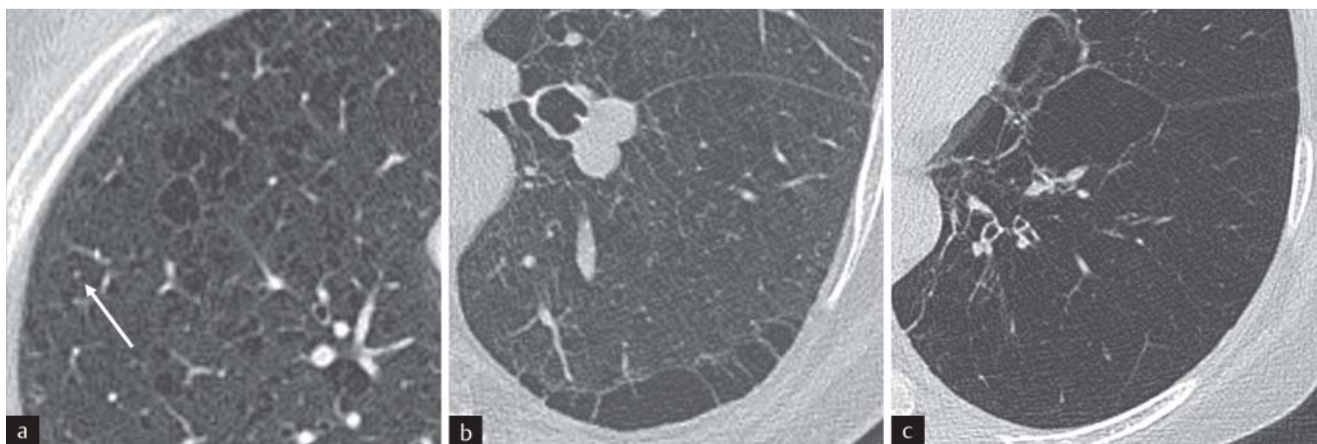


Fig. 2 Types of emphysema in relation to the secondary pulmonary lobule (HRCT sections). **a** Centrilobular emphysema (CLE). The process starts centrilobular with small focal lucencies without visible walls. The polygonal shape of some totally affected secondary lobules is clearly visible. The artery is seen as a white dot in the center (arrow). The interlobular septa build the margins containing pulmonary veins and lymphatics. **b** Paraseptal emphysema (PSE). Pulmonary lobules are affected peripheral, paraseptal and sub-

pleural. There are lucencies in a single layer with focal hyperinflation, in this case subpleural along the dorsal circumference. **c** Panlobular emphysema (PLE) due to alpha-1-antitrypsin deficiency. This type is characterized by uniform destruction of the entire pulmonary lobule with homogenous involvement of large parts of the lungs, mainly lower lobes. Normal parenchyma is barely visible, vessels are rarefied, lung is hyperinflated.

Radiological classification of emphysema

Anatomy

Emphysema is classified based on distribution within the secondary lobule, the smallest connective tissue anatomical subunit in the lungs. The lobule is polygonal in shape, measuring approximately 1–2.5 cm and is surrounded by connective tissue (interlobular) septa [8]. Under normal, healthy conditions, the lobule can only be detected on CT through inference. Running through the center of the lobule are the artery and the accompanying bronchiolus. Each lobule comprises on average 12 acini, each acinus in turn containing roughly 200 alveoli. While terms lobular and acinar are often used synonymously in describing a type of emphysema, the reference to the lobule is more appropriate from a radiological viewpoint, since only this part is visible. There are three main types of emphysema [9, 10]: centrilobular, paraseptal (formally known as distal acinar) and panlobular emphysema (Fig. 2). The Fleischner Society is currently developing a new method of classifying emphysema based on severity [11]. While further descriptive terms exist, they do not constitute unique subtypes: the (large) bullous emphysema, scar emphysema (vicarious emphysema) and a compensatory overexpansion emphysema (e.g. following contralateral pneumonectomy). The term “elderly emphysema” is considered to be obsolete and should not be used to describe the physiological alveolar hyperinflation not involving destruction in the senile lung [12].

Centrilobular emphysema

Centrilobular emphysema (CLE, adopted from the Fleischner Society) is the most common type. It appears mainly in smokers, affecting primarily the superior lobe. The process begins in the center of the secondary lobule. On CT images it morphologically appears as round density reductions without a wall that look like small “holes” in the surrounding initially still healthy lung parenchyma. This finding progresses toward the periphery until the entire secondary lobule

is involved. In advanced cases, multiple lobules are affected, which can progress to confluent involvement of the entire lobe and extensive parenchymal destruction (Fig. 3).

Paraseptal emphysema

With paraseptal emphysema (PSE) the peripheral, subpleural lobules are selectively affected. Density reductions and hyperinflations are visible along the pleura. The superior lobes are affected above all, e.g. resulting from scarring post-infectious shrinkage processes. This type of emphysema appears even in young nonsmokers and is frequently the cause of spontaneous pneumothorax.

Panlobular emphysema

Panlobular emphysema (PLE) is typical in patients with alpha-1 antitrypsin deficiency and the term is reserved for this condition (for cases of advanced, originally centrilobular emphysema, the term confluent emphysema is more appropriate)

The entire lobule exhibits relatively homogeneous, panlobular destruction. In this context, the “pan” refers to the secondary lobule (pan-lobular) not to the lobe. This is important to note, since the terms lobule (the small subunit) and lobe (the pulmonary lobe) should not be confused in everyday clinical activity. The lobules are inflated and the blood vessels rarefied. Distribution within the lobes is not localized or focal, but rather uniform and usually extensive. It is the inferior lobes that are primarily affected.

Bulla

A bulla is a sharply demarcated air-filled lesion greater than one centimeter in diameter (smaller lesions are called “blebs” = bubbles) with a delicate wall measuring less than one millimeter thick [13]. The disease is referred to as bullous emphysema when bullae are prominent. Giant bullae can measure more than 10 cm and take up a large volume, while compressing the surrounding lung parenchyma.

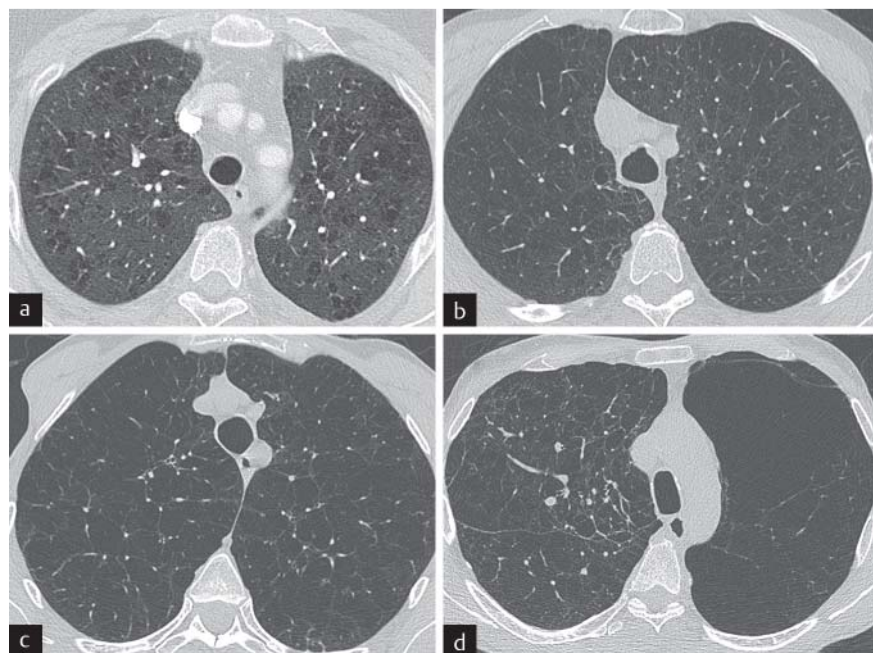


Fig. 3 Centrilobular emphysema of various severities. **a** Mild, with some small spotty centrilobular areas of emphysema, about 0.5 to 5 % of the upper lobe, surrounded by normal parenchyma. **b** Moderate, with less affected regions scattered next to larger areas of destruction. **c** Confluent, with centrilobular and lobular parts, without relevant hyperexpansion, or destruction of the lung architecture. **d** Advanced destructive emphysema with marked hyperextension and destruction of the lung anatomy not caused by alpha-1-antitrypsin deficiency (derived from Fleischner Society).

What every radiologist should know about emphysema therapy

Standard therapy for COPD, comprises, in addition to strict smoking cessation, medications such as bronchodilators and, if necessary, steroids, physical therapy, rehabilitation measures, later long-term oxygen therapy and, if necessary, non-invasive ventilation. However, the lung tissue already transformed by emphysema is irreversibly damaged. Due to the absent gas exchange surface and progressive dynamic pulmonary hyperinflation, patients in advanced stages suffer from serious dyspnea even under the most minor physical strain. In addition there are various (above all cardiovascular) comorbidities. Only after maximum conservative therapy has been exhausted, is a lung volume reduction (LVR) discussed as final stage therapy.

Principle of lung volume reduction

The idea of LVR, according to which the non-functional or pathologically hyperinflated “bloated” portions of the lung are (surgically removed) or deactivated, has existed as form of emphysema therapy for years. The objective is to achieve decompression to restore breathing space for the less affected portions of the lungs. The flattened diaphragm, which has been pressed downward, can recover and regain its rounded form. Breathing mechanics are boosted, the elastic resilience of the lungs improved and dyspnea decreased.

Surgical LVR

Surgical LVR was performed as early as the 1950s. At that time, the surgery was in no way equivalent to a simple bullectomy. The high peri- and postoperative mortality initially prevented the procedure from becoming established. However, it became the subject of research once again in the 1990s. The NETT study compared bilateral surgical LVR (usually performed by means of median sternotomy) with drug therapy between populations of 608 and 610 patients, respectively [14]. The 90-day mortality rate for the surgical

group was clearly elevated at 7.9% versus 1.3%, especially in cases of homogenous emphysema and forced exhalation (FEV1) values below 20% of the target. On the other hand, the patients with superior lobe emphysema and not capable of performing physical exercise benefited.

Subsequently developed minimally invasive, bronchoscopic LVR approaches are currently the subject of intensive study and examination [15–17]. In the wake of encouraging results, focus has shifted back to surgical treatment of emphysema (LVRS, lung volume reduction surgery) following years of restrained use.

Video-assisted thoracoscopic surgery (VATS) and median sternotomy exhibit comparable efficacy and safety, while involving a shorter hospital stay than VATS [18]. Study approaches are “staged VATS” (in which both side undergo two consecutive unilateral surgical interventions), a “non-resectional” LVR (clamping without actual resection of lung tissue) or laser resection. Thus far, no results are available for direct comparison between LVRS and endoscopic LVR, and the significance of LVRS is currently not clearly defined.

Endoscopic lung volume reduction (ELVR)

Over the last 10 years different bronchoscopic methods (Fig. 4) aimed at collapsing or shrinking the emphysematous lung tissue have been developed. These methods are an option only for patients with advanced stages of the disease and require an exhaustive diagnosis of lung function. Derived from the VENT-study [19], the inclusion criteria comprises, among other factors, stage 3 (through 4) COPD according to GOLD with high-grade pulmonary hyperinflation (residual volumes over 200%). In principle, distinction must be made between blocking and non-blocking as well as between reversible and irreversible procedures. Currently established methods are compared in Table 1.

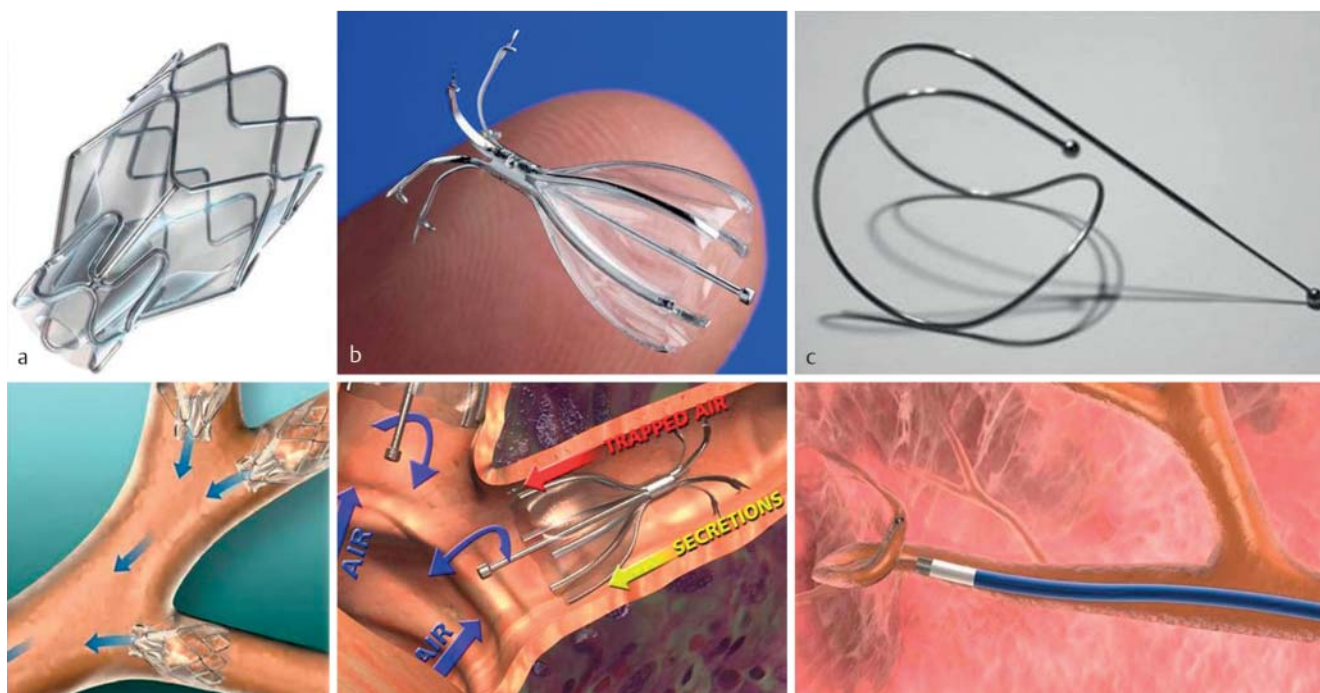


Fig. 4 Valves and coils. **a** Endobronchial Zephyr® valve (courtesy of PulmonX). **b** Intrabronchial Spiration® valve (courtesy of Olympus). **c** RePneu coils (courtesy of PneumRx). Bronchoscopic use is demonstrated in the bottom row.

| | valves | coils |
|--|--|---|
| technique | one-way valves allow air to leave but not enter the lung, causing a collapse of the target lobe; dynamic hyperinflation is reduced | shape-memory coils with mechanical action and tissue compression; elastic recoils are restored, air trapping is reduced |
| method | blocking | non-blocking |
| reversibility | reversible, removable | questionable |
| before ELVR | | |
| type of emphysema | heterogenous emphysema | both heterogeneous and homogeneous emphysema |
| target area | important | less important |
| fissures | integrity is crucial | not relevant |
| collateral Ventilation (CV) | CV is the main problem | non interfering |
| contraindication | large parenchymal destruction | pulmonal hypertension, giant bullae, large parenchymal destruction |
| after ELVR | | |
| atelectasis | atelectasis should be achieved | no atelectasis |
| residual parenchyma in the target lobe | gets lost | is preserved |
| pneumothorax | often | rare |
| hemoptysis | rare | often |
| migration | possible | rare |

Table 1 ELVR- Comparison of valves and coils.

Valves

Via the working canal of a bronchoscope, multiple valves are implanted in the segmental-, if necessary subsegmental bronchi as well, of a pulmonary lobe. Placement of a valve takes only a few minutes. A valve mechanism then prevents new air from flowing into the lungs, while still allowing the "old" air to flow out, thus collapsing the pulmonary lobe (Fig. 5). The goal is complete atelectasis of the treated lobe. As of now two different types of valves for this blocking, reversible method are available on the European market.

Endobronchial valves (EBV)

EBV (Zephyr® valves from PulmonX) comprises a silicone body surrounded by a nitinol wire cage (Fig. 4a). The end pointing in the proximal direction (toward the trachea) has a narrower diameter ("neck") with a "fish mouth" valve. The initial results were published in 2003 [20]. The data of the prospective VENT study in 2006 [29] initially showed only moderate benefits. In the meantime, the critical importance of patient selection has become clear. According to the EuroVent-Study [21], predictors of successful EBV therapy

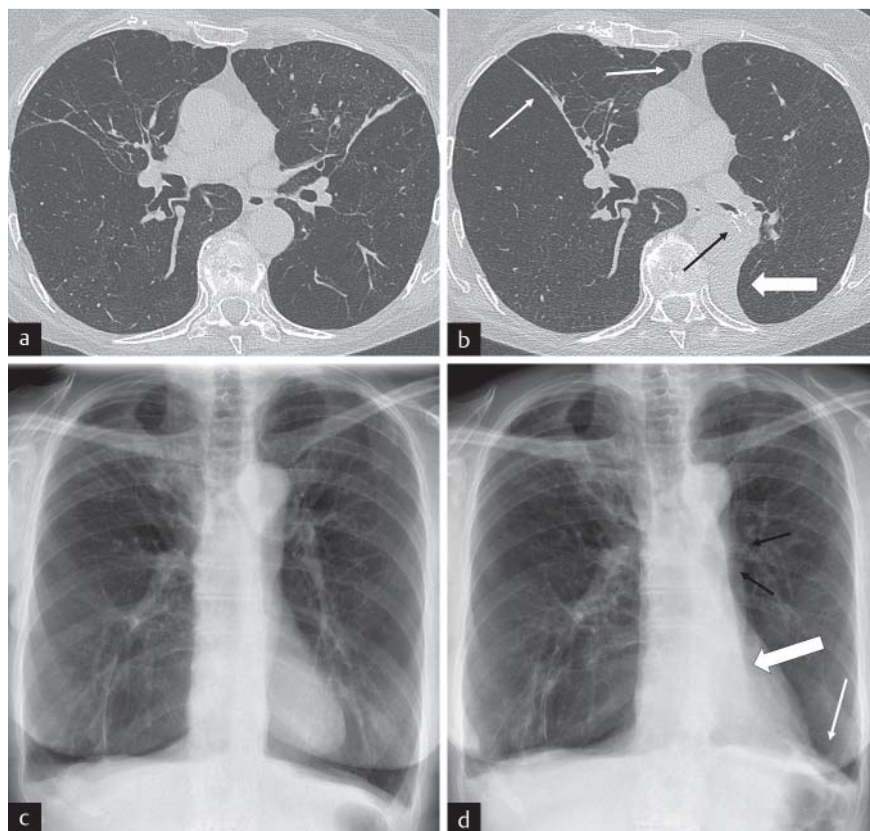


Fig. 5 Imaging before and after ELVR with valves. **a** HRCT before implantation of valves. **b** HRCT after implantation of valves. After placement of 4 valves into the left lower lobe the patient developed a lobe atelectasis as expected (thick white arrow). This section shows one of the valves in a good position with the “narrow neck” at the proximal end (black arrow). On the right side fissural and mediastinal shift is visible (thin white arrows). **c** Chest radiography pre-treatment (same patient). Normal middle position of the mediastinum, depression and flattening of the diaphragm. **d** Chest radiography after implantation of valves. On the left hilar region the filigran mesh of the valve is hardly seen on hard copy films (black arrows) but good on monitors. Left lobe atelectasis and mediastinal shift to the left (thick white arrow). The actual level of the left hemidiaphragm is slightly more apical as a sign of reexpansion (thin white arrow).

are a heterogeneous lung emphysema, correct placement and intact fissures.

Intrabronchial valves (IBV)

IBV (Spiration® valves from Olympus) resemble small umbrellas (◉ Fig. 4b). They are anchored via the distal feet (“anchoring hooks”), and the leaves attach to the walls of the bronchia. At the proximal end is a type of “stem” by which the valve can be gasped for removal if necessary. The unilateral complete occlusion of a lobe appears to be superior to a bilateral only partial occlusion [22].

According to user instructions, both types of valves are conditionally safe with MRI, i. e. a patient with this implant can safely undergo an MRI examination with a static magnetic field up to 3 Tesla [23, 24].

Metal spirals, “coils”

Wire spirals made of nitinol (a biocompatible nickel/titanium alloy) with a shape memory (RePneu® Coils from PneumRx) are used (◉ Fig. 4c). With the aid of a special implantation system, the wires measuring roughly 10 to 15 cm long are first introduced into the segmental bronchia under fluoroscopy, usually 10 units (if necessary more) being implanted in the selected lobes. Upon being released, the wires resume their original spiral shape (◉ Fig. 6), thereby pulling the bronchia together with the lung tissue to the hilum through mechanical force. A certain compression of the pulmonary parenchyma is achieved, the actual goal being the improvement of the elastic restoring forces. These non-blocking, debatably reversible methods do not result in atelectasis. The latest results show this method to be effective on heterogeneous and homogenous emphysema [25]. The

product received the CE label in October 2010 and is MRI-compatible up to 3.0 Tesla [26].

Additional methods: Vapor, gel and stents

Other irreversible, non-blocking methods include the introduction of hot water vapor (bronchoscopic thermoablation) or hydrogel foam (“bronchial adhesives”, polymer LVR or BioLVR) to systematically induce inflammatory stimulation in the most intensely affected area of the lung [27]. The goal is an acute, but “controlled” inflammatory process with subsequent shrinkage of the tissue through scarring or fibrosis. Although a meta-analysis [28] showed the best results for BioLVR, this method is currently no longer available. Thermoablation is still considered to be experimental, since there have been no major studies [29]. Endoscopic creation of artificial airways by means of needle perforations (airway bypass) has been suspended due to complications (EASE-study) [30].

What pulmonologists expect from radiological imaging and reporting?

▼ X-ray/CT/MRI?

According to the guidelines of the German Respiratory Society (Deutschen Gesellschaft für Pneumologie), a chest X-ray in two views should be performed for general diagnostics when COPD is initially diagnosed. The validity of the criteria for emphysema already defined in 1965 was confirmed once again by Miniati et al. 2008 [31]. We routinely see flat, low-lying diaphragmatic arches, increased lung transparency, and enlarged retrosternal space as well as ex-

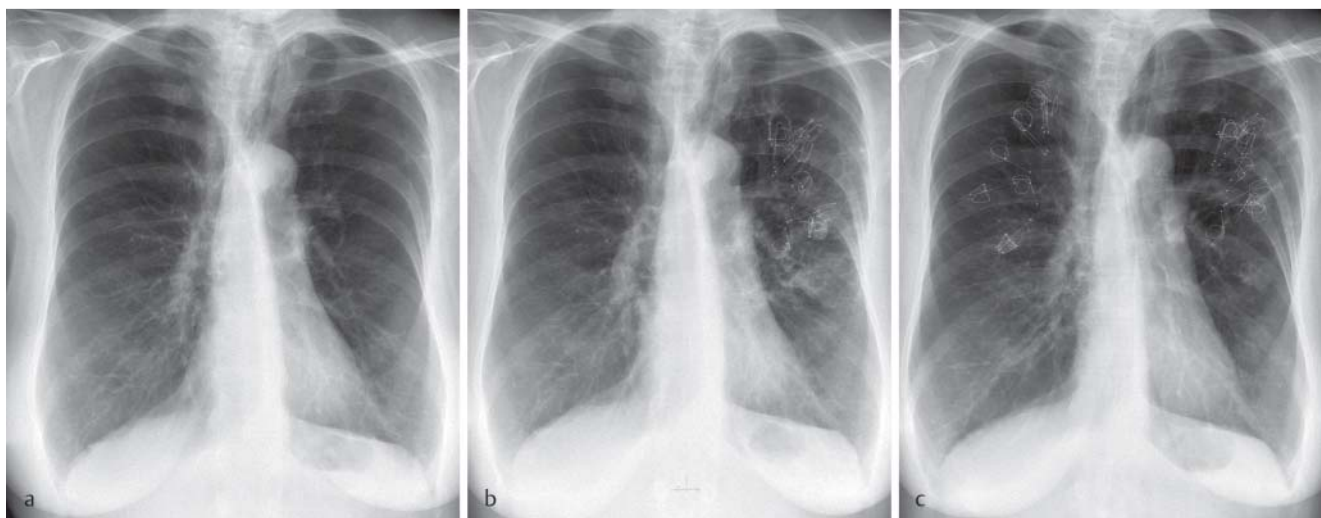


Fig. 6 Chest radiography before and after ELVR with coils. **a** Pre-ELVR. **b** After treatment with coils in the left superior lobe. **c** After treatment with coils in the superior lobes, bilateral.

panded intercostal spaces, a barrel chest and, as the case may be, a teardrop-shaped, narrow heart silhouette. However, when dealing with mild forms of emphysema, this method is not sufficient for determining distribution and is in no way suited for testing whether ELVR is indicated.

The lungs present a challenge for MRI, since they have a very low proton density compared to the brain, liver or musculature, and the margins between the air and parenchyma lead to susceptibility artifacts. Breathing and heartbeat additionally create motion artifacts, thereby necessitating rapid sequences, parallel imaging as well as breathing and EKG triggering [32]. In the majority of cases, there is agreement between MRI and CT in classifying emphysema and evaluating the severity thereof [33]. On the other hand, the morphological and functional magnetic resonance imaging of COPD with visualization of ventilation, breathing dynamics and perfusion is becoming increasingly prominent [34]. Dynamic MRI during continued breathing is excellent at showing how severely diaphragmatic mobility is restricted in cases of emphysema [35]. The phenotyping of COPD using MRI and low-dose CT is currently being compared in a multicentric, national cohort study (Cosyconet) [36]. However, the lengthy examinations and long periods of having to hold their breath still remain difficult for patients who already suffer from dyspnea due to their underlying disease.

Without a doubt, CT of the lungs is currently the method of choice. Pulmonologists expect a non-contrast, high-resolution spiral CT taken during inspiration. If disease of the minor airways is suspected, sequential scans during expiration should additionally be performed.

The technical prerequisite is a 3rd generation or above multi-detector CT with at least 16 lines, the standard being 64-lines (if necessary 40 lines). According to definition, slice thickness for a HRCT should be less than 1.5 mm [8]. A slice collimation below 1 mm (depending on manufacturer, e.g. 0.6 mm) with as low of a rotation period as possible (≤ 0.5 s), an increment of 0.7 and an overlap of 30–50% is recommended. In CT protocols of the thorax there are considerable differences in current exposure time product

(40 mAs to 200 mAs) [37]. Low-dose data sets with a current exposure time product of just 30 to 50 mAs allow both a visual and quantitative evaluation of the emphysema [38]. In contrast, a higher dosage is necessary for the analysis of the airways particularly in the case of software-assisted evaluations. For example, the median effective current exposure time product in the COPD Gene Study was 180 mAs [39]. In our scan protocol, tube current was 100 mAs and tube voltage 120 KV. To reduce radiation exposure, automatic dosage modulation was employed. Iterative image reconstruction techniques are also highly promising. While the image quality suffers when dosage is reduced by 50% and data sets are reconstructed by means of filtered back-projection (for example, because of the increased noise pattern the differentiation between residual lung parenchyma and bulla was compromised), iterative reconstruction technique allows a comparable image quality to be achieved at half the radiation dose [40].

Generating sagittal and coronal 3D reconstructions is especially important, with reconstructed slice thickness of ≤ 1.5 mm also being ideal in this case. A differentiated evaluation of findings focusing on the following diagnosis- and therapy-relevant criteria is required.

Quantification of the emphysema

In routine clinical practice, the individual patient's complaints do not accurately foreshadow the morphology or severity of the emphysema revealed through CT, although the extent of the emphysema correlates with the severity of COPD at least in cases of centrilobular and panlobular, but not paraseptal type. In addition to the purely quantitative description in the report, an assessment that is as standardized, objective and reproducible to the extent possible is required. Lung density measurements using Hounsfield units (HU) and an estimate of the extent of emphysema as a percentage (e.g. 0%, below 5%, up to 25%, up to 50%, up to 75%, over 75%) are helpful in this respect [42]. Visual assessment is performed separately for the individual lobes of the lungs. The examiner-dependent variability remains problematic [41–43].

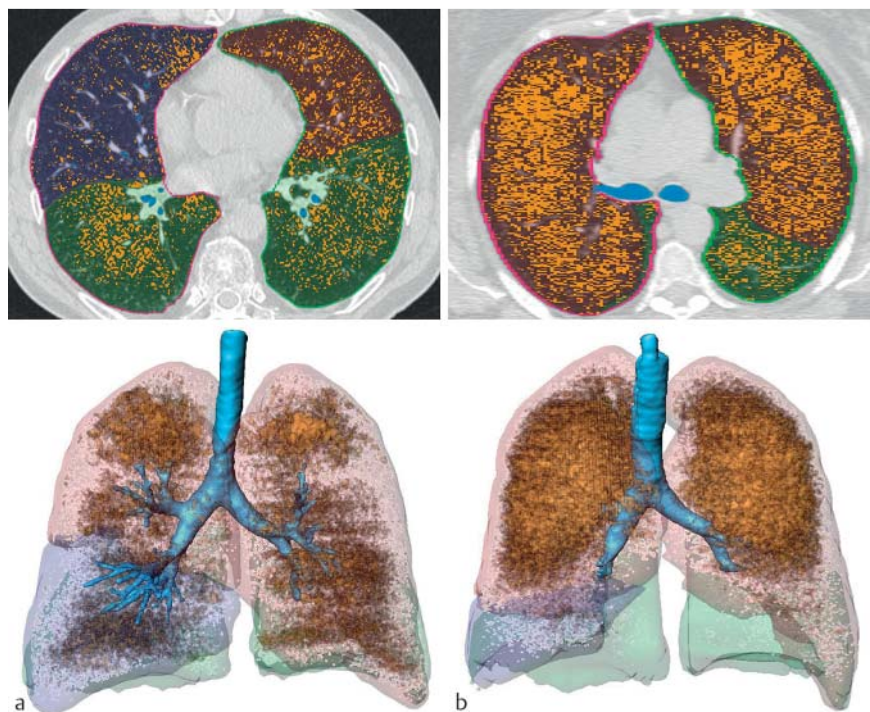


Fig. 7 Software analysis of emphysema. Areas with low attenuation are depicted in orange indicating centrilobular emphysema. Upper image shows axial HRCT scan, 3D-rendering is seen in lower image. **a** Heterogeneous distribution, all lobes are affected, no explicit predominance. **b** Marked predominance of emphysematous regions in both upper lobes, possible target areas for ELVR. (Courtesy of Fraunhofer MEVIS, Bremen).

CT-densitometry can be performed semiquantitatively or quantitatively (computer-assisted) [44]. Evaluation is reportedly made easier with specialized software which shows emphysematous areas marked in color (e.g. as color map) on the basis of a prescribed density limit value and generates a table summarizing density values. The average lung density (expressed in HU) can be computed from the density values of all lung voxels, while segmentation of the lung margins is fully automatic. The emphysema index can be computed as a quotient of emphysema volume and lung volume (expressed in percent). Several programs are already commercially available (• Fig. 7). However, there are major differences in the different types of software, among which are the evaluation and presentation of data. While the results were still disappointing in 2006, e.g. the considerable amount of time required and the poor correlation between human eyes and the machine [45], by 2014 it was more than clear that qMDCT (CT densitometry using multi-detector-row computed tomography) represents a diagnostic gain [46]. However, it remains unclear how strongly patient-related factors (age, inspiration depth) influence the measured values. In addition, a uniform threshold value for density measurement has not yet been established (initially -910 HU, then -970 HU, now usually -950 HU) [47]. Moreover, the computer-based segmentation of the individual lobes of the lung is still not reliable [48], and areas with increased density such as dystelectases and infiltrates are problematic. Serious differences in terms of evaluation appear depending on the CT scanner used, the reconstruction parameters and, above all, the software manufacturer [48]. The indication of the “PD 15” value – the lung density of the 15th percentile when showing the relative frequency of all measured voxel densities in a histogram – is highly promising. With emphysema, the low density values shift the HU distribution curve to the left and into the negative region. The EXACTLE study examining alpha-1 antitrypsin defi-

ciency demonstrated that CT densitometry can represent a valid endpoint in a longitudinal study [49]. Unfortunately, no broadly available, reproducible standard has yet been established for software-based diagnosing of emphysema.

Target area

Only with the aid of radiology can the distribution of emphysema and the heterogeneity thereof be evaluated. A multidisciplinary approach must be employed to determine whether or not a target area exists. Emphysema being prominent in a lobe of the lung with hyperinflation or disproportionately high volume, e.g. visible in the form of a displacement of the lobe fissures and mediastinum, would be ideal. In contrast, giant bullae or an excessively extensive destruction of the parenchyma if anything impede endoscopic measures, since the presence of consecutively larger hollow spaces poses the risk of uncontrolled tissue tearing. The quantity and quality of the residual parenchyma are not irrelevant. The idea behind the valves is to remove all air from the target lobes and achieve atelectasis of a lobe to reduce as much volume as possible. In this process, however, the lobe is completely “deactivated”, and its remaining parenchyma is no longer available for gas exchange. With the coils, in contrast, the residual tissue is “preserved” and can continue to function for gas exchange, since the target lobe remains ventilated. In cases of homogeneously distributed emphysema, valves are at least not recommended. In addition, pre-interventional lung perfusion scintigraphy is recommended for estimating the loss of function following treatment of the target area. MRI of lung perfusion can also be expediently used to diagnose diseases of the airways and lung parenchyma [50]. For planning LVR, the areas of the lungs with impaired function can be visualized with the advantage of higher spatial resolution, combined imaging of morphology and function as well as absence of ra-

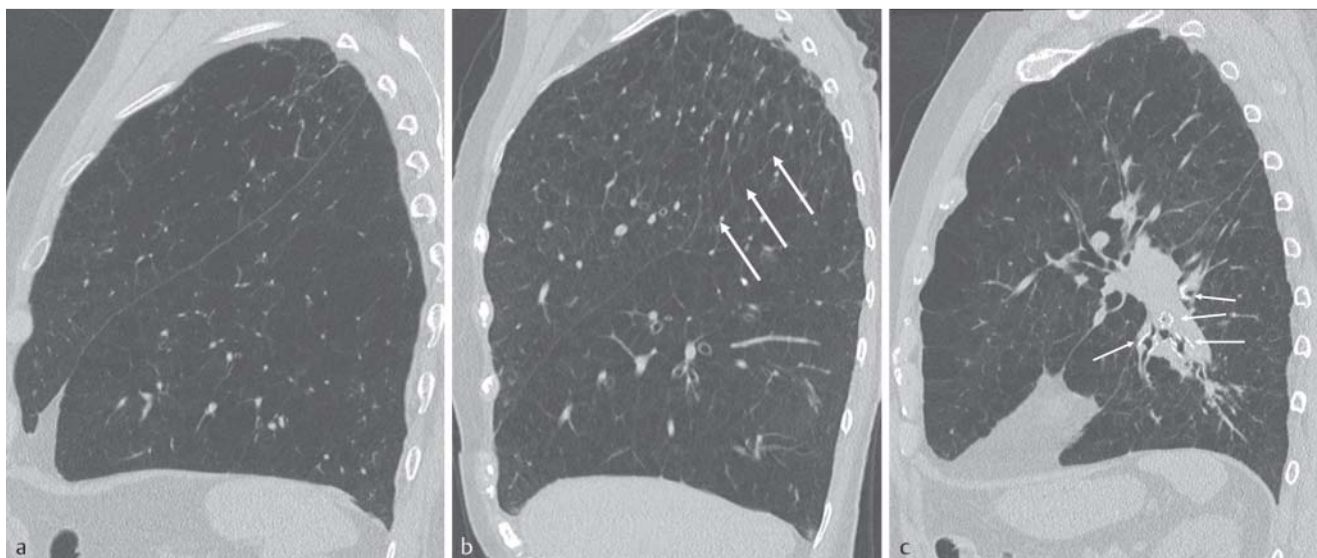


Fig. 8 Fissural analysis as a selection criterion for ELVR (HRCT, sagittal reconstruction). **a** Complete fissure. Visualization of the interlobular fissure as a contiguous sharp fine line, no obvious parenchymal bridges between superior and inferior lobe, thus no clear sign for collateral ventilation in this section. **b** Incomplete fissure. The fine interlobular line is disrupted in the apical portions. The course of the fissure is no longer visible (arrow). Broad

parenchymal bridges between upper lobe and inferior lobe, collateral ventilation is very likely. **c** Absent atelectasis after ELVR. Five endobronchial valves were implanted in the left inferior lobe. In this CT scan four of them are visible (arrows). A complete atelectasis of the inferior lobe was not achieved, probable retrograde ventilation due to collateral ventilation.

diation exposure. As a result, this method can also be used to assess the course of the disease following LVR.

Fissure analysis: The interlobular fissures

CT examinations performed following valve implantations have shown that the desired atelectasis is frequently not achieved, can have a delayed onset or is only temporary [51]. The main reason for this would be what is referred to as collateral ventilation (CV), i.e. even if the valves are placed correctly and good occlusion is established, a retrograde reventilation of the treated lobe occurs via parenchymal bridges from the neighboring lobe [52]. This process hinders the actual volume reduction. It is now known that CV is an important selection criterion. Radiology provides answers by allowing analysis of the interlobular fissures (● Fig. 8). A normal left lung has only one fissure, while the right has an oblique fissure (lower fissure) and horizontal fissure (upper fissure, running horizontally between the superior lobe and middle lobe). Visualizing the pulmonary fissures as continuous, sharp lines requires a collimation of 0.5 to 1.0 mm [53] along with sagittal and coronal multiplanar reconstructions. A radiologically imaged continuous “complete” fissure is an indirect sign of an absent or minor CV. In a small study involving 25 patients, 20 of 21 pulmonary lobes having collateral ventilation also showed a defect in the fissure, with sensitivity being 95%. However, specificity was only 44%, i.e. 7 of 16 evaluated lobes without collateral ventilation had no fissure interruption on CT [54].

What constitutes a complete or incomplete fissure remains problematic, as neither has yet been uniformly defined in terms of CT morphology. As a result, the reported occurrence of incomplete fissures greatly fluctuates in the literature between 20% and 87%. Automatic fissure analysis methods are currently being developed [55].

A computer-assisted analysis of 573 CT-examinations recently showed that roughly 90% of all examined persons have incomplete fissures regardless of whether COPD is present or not [56]. For the individual fissures, integrity was around 82% for the oblique fissures (bilateral) and 62% for the horizontal fissure, regardless of severity of COPD. Integrity of 90–100% was defined as “complete” (continuous, intact fissure) and was present in only a quarter of patients, left 25%, right 26% (oblique fissure) and 14% (horizontal fissure). Contradicting these findings, an analysis of 250 CT images with a by far higher portion of intact fissures showed the left fissure to be incomplete in only 24.4% of cases (thus appearing continuous in three quarters of all patients), and the right fissure incomplete in 35% of cases. [57]. There is a consensus regarding at least the horizontal fissure, which very frequently appears to be uninterrupted, as well as regarding the perihilar region, which is more difficult to evaluate and is where parenchymal bridges tend to form. The clinical significance of “small” parenchymal bridges (appearing in approximately one third of patients [58]) as well as accessory fissures (appearing in 16% of patients, primarily in the superior lobes [57]) on CV has not been clarified.

Collateral ventilation can also be measured through bronchoscopy using a balloon catheter. This can be performed in a procedure immediately prior to ELVR. A reduction of lung volume can be forecast with an accuracy of approximately 75% using the Chartis® evaluation system. However, this method does not replace CT. A prospective study is currently being conducted to determine whether the clinical benefit can be predicted when a homogenous emphysema with intact fissure is diagnosed using CT [60]. Overall, fissure analysis using CT must be viewed cautiously for the time being. In addition to a thorough scanning in all three planes, a uniform classification is urgently required

| checkpoint | | note | |
|-------------------|----------------------|---|--|
| image acquisition | | high-resolution multidetector CT of the lungs without contrast spiral technique, contiguous, slice thickness 1.0 to 1.5 mm 3 D reconstructions in axial, coronal and sagittal orientation submission of images via CD/DVD | |
| phenotyping | airway-type | bronchitis? bronchiolitis? mucus? bronchiectasis? instability of airways? | |
| | emphysema-typ | centrilobular, paraseptal, panlobular giant bullae? | |
| | | extension: mild, moderat, confluend, large destructions if available: specified as a percentage if available: automatic quantitative assessment | |
| | | distribution: homogeneous, heterogeneous if available: heterogeneity-/emphysema-index | |
| before ELVR | target area | yes (where?)/no | |
| | fissure-integrity | major and minor fissur: contiguous line? gaps? careful inspection in all directions including MPR | |
| | contraindications | pulmonal hypertension? pneumonia? | |
| | relevant pathologies | Lung cancer, pleural thickening, pleural effusion, ... | |
| after ELVR | ELVR-device | valves or coils visible? number of devices compliant to anamnesis? implantation in correct side/ correct segment bronchi? occlusion of the bronchi? migration/aspiration/dislocation? correct position? EBV: narrow end ("neck") points to the proximal IBV: the "5 arm anchor tip" points to the distal coils: about 2 cm distance to pleura | |
| | | LVR-effect | volume reduction effect? atelectasis? mediastinal shift? fissural shift? reexpansion of the diaphragma? |
| | | complications? | pneumothorax? infiltration? hemorrhage? |
| | | new target area? | yes/No |

Table 2 Checklist for Imaging for ELVR.

for defining an intact fissure and assessing collateral ventilation.

Routine clinical experiences with ELVR

For adequate treatment of emphysema, radiologists and pulmonologists must work together as a team. While careful patient selection on the basis of clinical findings and imaging is critical, it is not yet sufficiently practiced at all intuitions. In the meantime, the results following ELVR are increasingly coming to our attention in cases of, for example, valves becoming dislocated or having to become removed due to complications.

Among the frequent complications following ELVR are exacerbation of COPD and infections, including pneumonia. Caution is thus urged for patients with hypersecretory bronchitis, as the valves can be displaced by the secretion. Before undergoing ELVR, patients should be free of bronchopulmonary infection, have no serious concomitant disease and be mobile and clinically stable. The patient must also be able to tolerate a pneumothorax in the pulmonologist's medical opinion, since the occurrence thereof must be anticipated as a result of the at times enormous tractive forces following ELVR. On radiological images, these forces are indicated by post-interventional migration of the fissures and the mediastinum. Extensive tissue destruction and giant bullae can be problematic prior to ELVR, constituting a contraindication for the insertion of coils. Instead of valves, surgical LVR would be a better option to discuss. Because of the risk of bleeding, coils are also contraindicated for patients on

anticoagulation therapy or suffering from pulmonary hypertension. Post-interventional hemoptysis is typical following the implantation coils, yet is usually easily managed. In addition to patient selection, good management of complications in a center is the key to success.

Summary

Today, the implantation of valves or coils is well established at many centers. Technically relatively simple to perform, ELVR remains a purely symptomatic treatment for carefully selected advanced stage patients, which should ideally be performed at experienced centers and tracked in studies. Because the primarily promising therapy procedure prompts a lack of caution, an interdisciplinary discussion among pulmonologists, thoracic surgeons and radiologists is key for optimized patient selection. Finally, a checklist was created which is intended to aid during radiological diagnostic testing before and after ELVR (• **Tab. 2**).

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