Lung Volume Reduction in Pulmonary Emphysema from the Radiologist's Perspective

Lungenvolumenreduktion beim Lungenemphysem aus der Sicht des Radiologen

Authors F. Doellinger[1], R. H. Huebner[2], J. M. Kuhnigk[3], A. Poellinger[1]

Affiliations
[1] Department of Radiology, Charité Universitätsmedizin Berlin, Germany
[2] Department of Internal Medicine/Infectious and Respiratory Diseases, Charité Universitätsmedizin Berlin, Germany
[3] Institute for Medical Image Computing, Fraunhofer MEVIS, Bremen, Germany

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Correspondence
Dr. Felix Döllinger
Department of Radiology,
Charité Universitätsmedizin Berlin
Augustenburger Platz 1
10117 Berlin
Germany
Tel.: ++ 49/30/4 50 62 71 09
Fax: ++ 49/30/4 50 62 71 09
felix.doellinger@charite.de

Abstract

Pulmonary emphysema causes decrease in lung function due to irreversible dilatation of intrapulmonary air spaces, which is linked to high morbidity and mortality. Lung volume reduction (LVR) is an invasive therapeutical option for pulmonary emphysema in order to improve ventilation mechanics. LVR can be carried out by lung resection surgery or different minimally invasive endoscopical procedures. All LVR-options require mandatory preinterventional evaluation to detect hyperinflated dysfunctional lung areas as target structures for treatment. Quantitative computed tomography can determine the volume percentage of emphysematous lung and its topographical distribution based on the lung's radiodensity. Modern techniques allow for lobebased quantification that facilitates treatment planning. Clinical tests still play the most important role in post-interventional therapy monitoring, but CT is crucial in the detection of postoperative complications and foreshadows the method's high potential in sophisticated experimental studies. Within the last ten years, LVR with endobronchial valves has become an extensively researched minimally-invasive treatment option. However, this therapy is considerably complicated by the frequent occurrence of functional interlobar shunts. The presence of "collateral ventilation" has to be ruled out prior to valve implantations, as the presence of these extra-anatomical connections between different lobes may jeopardize the success of therapy. Recent experimental studies evaluated the automatic detection of incomplete lobar fissures from CT scans, because they are considered to be a predictor for the existence of shunts. To date, these methods are yet to show acceptable results.

Key points:
- Today, surgical and various minimal invasive methods of lung volume reduction are in use.
- Radiological and nuclear medical examinations are helpful in the evaluation of an appropriate lung area.
- Imaging can detect periinterventional complications.
- Reduction of lung volume has not yet been conclusively proven to be effective and is a therapeutical option with little scientifc evidence.

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Zusammenfassung

Beim Lungenemphysem kommt es durch die irreversible Erweiterung intrapulmonaler Lufträume zu einer Einschränkung der Lungenfunktion, die mit hoher Morbidität und Mortalität einhergeht. Die Lungenvolumenreduktion (LVR) stellt eine invasive Therapieoption des Lungenemphysems dar, durch die eine Verbesserung der Atemmechanik erzielt werden soll. Eine LVR kann chirurgisch mittels Lungenteilresektionen oder durch verschiedene minimalinvasive, endoskopisch vermittelte, Techniken erfolgen. Allen Verfahren ist gemein, dass die zu behandelnden Lungenabschnitte vor Therapiebeginn evaluiert werden müssen, um insbesondere chronisch überblähte, dysfunktionale, Areale behandeln zu können. Mit quantitativer Computertomografie können der relative Anteil der emphysematischen Lungenareale am gesamten Lungenvolumen und ihre topografische Verteilung anhand ihrer Röntgendichte reproduzierbar ermittelt werden. Moderne Techni-

ken ermöglichen eine lappengetrennte Quantifizierung des Lungenemphysems, mit der die Therapie geplant werden kann. Im postinterventionellen Therapiemonitoring haben weiterhin klinische Parameter entscheidenden Stellenwert, die CT dient jedoch der Detektion postinterventioneller Komplikationen und lässt in experimentellen Studien ihr Potenzial erahnen. Die in den letzten 10 Jahren ausführlich erforschte minimalinvasive LVR mit endoskopisch implantierbaren endobronchialen Ventilen ist durch das häufige Vorkommen funktioneller interlobärer Shuntverbindungen erheblich verkompliziert. Das Vorliegen einer solchen „kollateralen Ventilation" muss vor der Implantation der Ventile in einen Ziellappen ausgeschlossen werden, da die extraanatomische Verbindung einzelner Lappen sonst den Therapieerfolg gefährden kann. Experimentelle Studien beschäftigen sich mit der automatisierten Detektion inkompletter Fissuren aus CT-Untersuchungen, da diese als ein Prädiktor der Shunts angesehen werden. Dies gelingt aktuell jedoch noch nicht auf akzeptable Weise.

COPD and pulmonary emphysema

The term *chronic obstructive pulmonary disease* (COPD) is used to describe a group of diseases, the most important examples being chronic (obstructive) bronchitis and pulmonary emphysema. COPD is highly prevalent and involves a high rate of morbidity and mortality [1]. In Germany, roughly 5 to 10 % of the population over the age of 40 meets the criteria for diagnosis [2].

Pulmonary emphysema is defined histologically as a permanent, irreversible dilation of the air spaces distal to the terminal bronchioles destructive to the pulmonary anatomy without visible fibrosis [3]. Autopsy studies have demonstrated that emphysematous destruction up to 30 % of the lung volume is possible even if pulmonary function tests (PFT) show normal results [4]. Pulmonary emphysema can accordingly also exist in occult form.

In general, distinction is made between two different types of emphysema. Centrilobular emphysema involves a destruction of the small acinar bronchioles and the neighboring bronchioles, as is typically observed in smokers or as a result of chronic dust inhalation. Panlobular emphysema, in contrast, involves a destruction of the entire acinus without the anatomical structures of the central lobulus remaining intact, as is typical with alpha-1 antitrypsin deficiency, for example.

A normal relationship between pulmonary blood flow and ventilation provides the basis for sufficient gas exchange. In COPD patients with pulmonary emphysema, the ventilation of the alveoli decreased through bronchial obstructions and parenchymal destruction results in a hypoxic pulmonary vasoconstriction described as the Euler-Liljestrand reflex. The permanent loss of the small peripheral branches of the pulmonary arteries in emphysematous areas of the lungs is attributed, among other factors, to the mechanical compression of the small vessels by the hyperinflated lung parenchyma [5].

There is currently no therapy that treats the cause of pulmonary emphysema. The goal of available palliative symptomatic therapy options is to reduce the progression of the disease and mortality [6]. As the most important therapy option, smoking cessation can retard further deterioration of pulmonary function and improve survival in cases of emphysema [7]. COPD drugs primarily treat symptoms and facilitate barely any improvement in pulmonary function. In addition, conservative therapy options include vaccinations against influenza and pneumococci to prevent infectious exacerbations and improvement of physical fitness in exercise groups receiving treatment [6].

Treating pulmonary emphysema through lung volume reduction

According to the 2008 "BOLD" study, 0.8 % of COPD patients in Germany meet the criteria for GOLD stage III or IV COPD [8]. Patients in this group become potential candidates for lung volume reduction (LVR) once all conservative therapy options have been exhausted [6].

The effect of each LVR is manifested in a relief of breathing musculature resulting from improved breathing mechanics [9]. For this reason, it is particularly important to treat those dysfunctional areas of the lungs playing only a reduced role in gas exchange as a result of emphysematous hyperinflation [9]. Following effective LVR, the volume of dysfunctional, hyperinflated areas of the lungs decreases, followed by improvement of the ventilation-perfusion-index [10].

Surgical and multiple minimally invasive procedures currently coexist.

Lung Volume Reduction Surgery (LVRS)

While LVRS was first practiced in the 1950 s [11], it was not until the 1990 s that it was reintroduced by *Cooper et al.* [12]. The pathophysiological basis for the procedure is the improved expansion and ventilation of healthy regions of the lung following resection of chronically hyperventilated areas [11].

It is known that LVRS yields better clinical results in patients with apically focused "heterogeneous" emphysema than it does in patients with diffuse distribution [13], also known as "homogeneous emphysema". Published in 2002, the "NETT" Study (*National Emphysema Treatment Trial*) established that LVRS extended survival exclusively in patients with heterogeneously distributed, apically focused emphysema and high-grade limited physical capacity [14].

An important advantage of LVRS is that allows direct intraoperative examination of hyperinflated regions of the lungs. Additionally, partial lung resections can be performed not only along anatomical borders as lobe resections, but also extra-anatomically. The volume of especially damaged sections of a lobe can thus be reduced predominantly in a simpler manner than is possible with minimally invasive LVR procedures. However, a key limitation is posed by the limited view of the intraoperatively atelectatic lungs, making it considerably difficult for the thoracic surgeon to anatomically locate the emphysematous areas identified beforehand through CT.

Nevertheless, the most significant limitation of LVRS is the perioperative morbidity and mortality despite even the use of modern surgical methods [14]. Patients with COPD (FEV_1 and diffusions capacity for carbon dioxide (DLco) < 20 % of the expected value) are generally not candidates for LVRS,

with the "NETT" study showing this subgroup to have a high postoperative mortality risk of 9.7 % after 90 days [14]. However, if strict patient selection criteria are followed and the aforementioned subgroup is generally excluded, good postoperative results can be observed even in patients with homogenously distributed emphysema [15, 16].

Endoscopic Lung Volume Reduction (ELVR)

ELVR is a term for minimally invasive, bronchoscopy-assisted LVR procedures and currently includes both reversible therapies in the sense of one-way endobronchial valves and irreversible procedures such as the endobronchial application of hot steam and endobronchial coils.

Contraindications for ELVR, as defined in most studies, are active nicotine abuse, cardiovascular diseases with special emphasis on pulmonary hypertension, chronic infections of the lower airways, malignant tumors and psychosocial contraindications.

Occlusive Endobronchial Valves (EBV)

Clinical trials involving reversible endobronchial valves as minimally invasive LVR therapy commenced in 2003 [17, 18]. The advantage of these valves is that they can be removed entirely in the event of complications, e. g. (rare) retention pneumonia or pulmonary hemorrhage. On the other hand, EBV are not permanently anchored and can become dislocated from the force of coughing, and can even be coughed out. Made of the technical alloy nitinol and silicone, the occlusive valves are anchored in lobular or segmental bronchi via a bronchoscopic guide catheter. A "one-way mechanism" is designed to cause isolated atelectasis in the target area distal to the valve [19]. Correctly implanted valves open during expiration to allow the air to flow out of the areas of the lung distal to the valve. EBV are also designed to allow mucus, in addition to respiratory air, to escape from the downstream areas of the lungs to thereby decrease the risk of downstream pulmonary infections. During inspiration, the valve then closes to block the flow of respiratory air into the treated lobes, thereby successively reducing their volume. It is therefore necessary to always occlude an entire lobe, since intralobular segments are normally ventilated collaterally and such collateral ventilation would otherwise prevent atelectasis.

Fig. 1 shows the method of action of the endobronchial valves during inspiration and expiration using diagrams and bronchoscopic images taken in vivo.

There are essentially two manufacturing companies currently competing on the international market. The *Zephyr* valves from the US company *Pulmonx* typically feature a type of "duckbill mechanism", while the *Spiration* valves from the Japanese manufacturer *Olympus* employ a mini-umbrella design. The first clinical cooperation studies with *Olympus* were based on the idea of creating incomplete bronchial occlusion with the goal of being able to contain peri-interventional complications. This was not achieved, however, since the patients, while initially reporting subjective respiratory improvement, exhibited a drop in FEV_1 to below baseline during follow-up [20, 21]. In a prospective study involving 22 patients, *Eberhardt et al.* compared the complete occlusion of a lobe against a bipulmonary partial occlusion in which complete atelectasis is to be avoided. The clinically measurable therapeutic success in the sense of increased FEV_1 is significantly better with complete unilateral occlusion (change in FEV_1 by +21 % compared to +/- 0 %) [22]. The complete occlusion of a selected lobe is now the goal of each ELVR using EBV.

Although frequent, peri-interventional complications of EBV implantation are rarely fatal. In the "VENT" study (*endobronchial valve for emphysema palliation trial*) *Sciurba et al.* observed a significant increase in COPD exacerbations and pneumonia, hemoptysis and pneumothorax [19]. However, the incidence of post-interventional pneumothorax was primarily underestimated in the "VENT" study at 4.2 %, with more current publications estimating a risk of roughly 20 % for patients treated with EBV [6]. This can be attributed particularly to the improved patient selection in the mean-

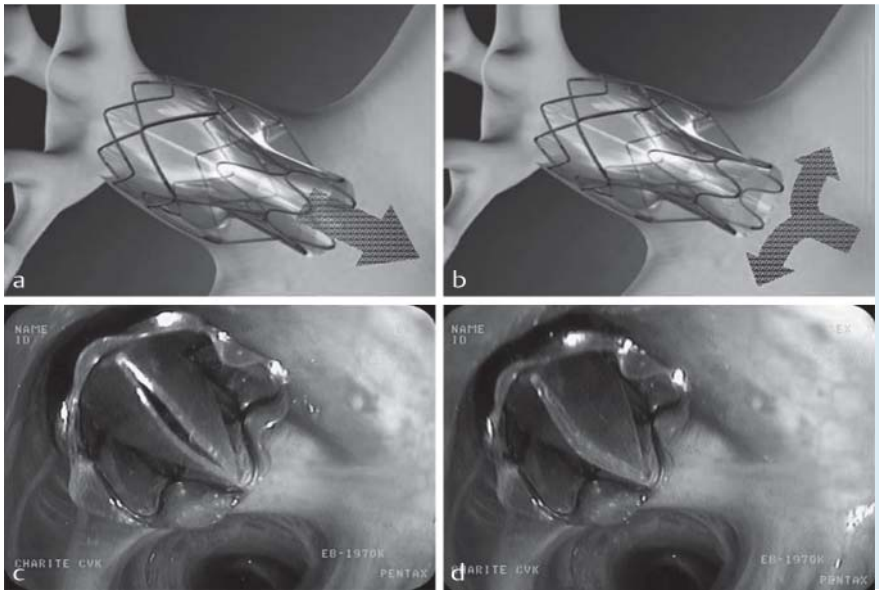

Fig. 1 shows the "one-way mechanism of the occlusive endobronchial valves. During expiration **a**, **c** the valve opens to allow the air to flow out of the areas of the lung distal to the valve. During inspiration **b**, **d** the valve closes to prevent the respiratory air from flowing back into the treated area of the lung. (The schematic drawings **a, b** courtesy of Pulmonx Inc., the bronchoscopic images **c, d** courtesy of RH).

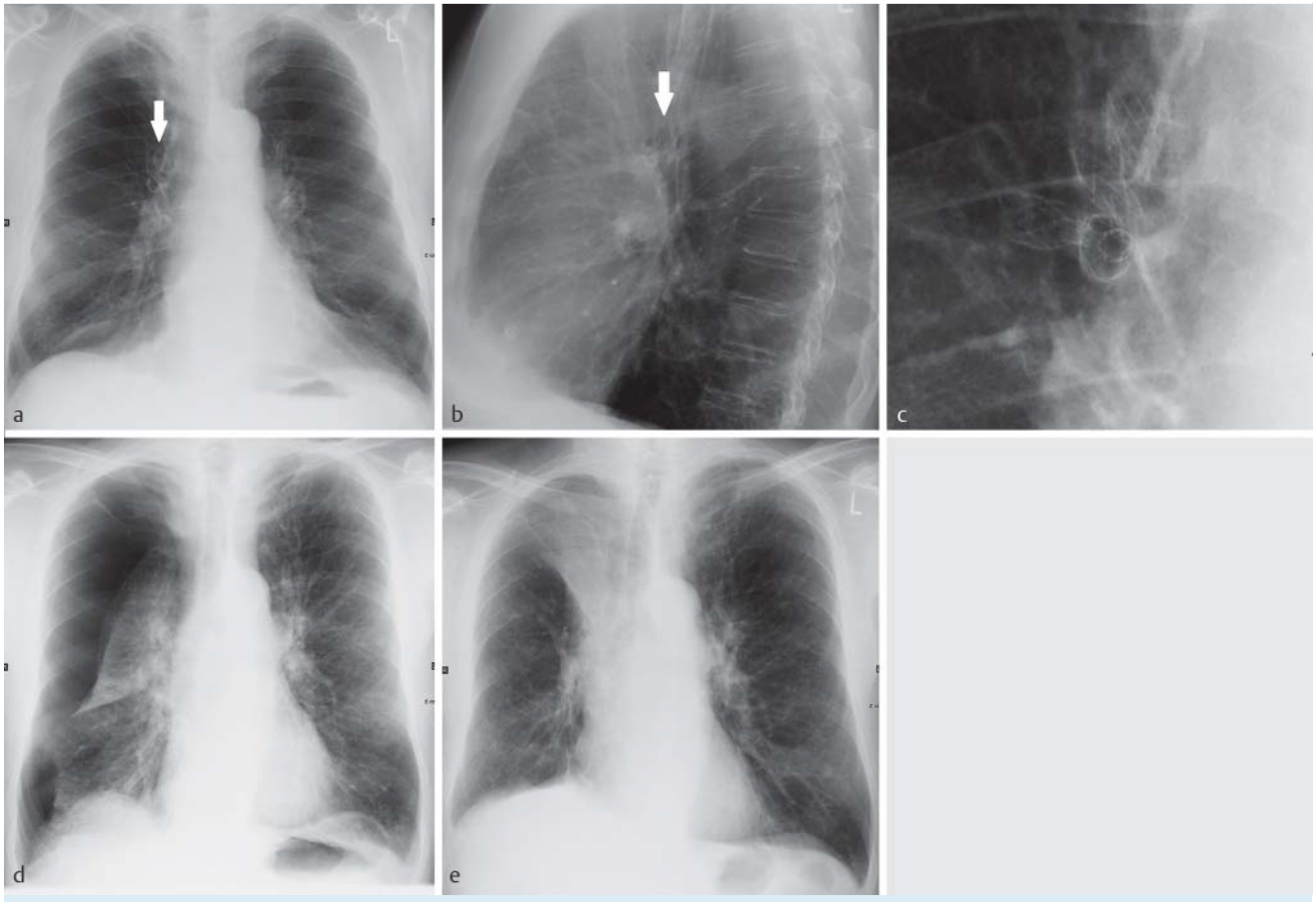

Fig. 2 shows radiographs of endobronchial valves. **a–c** shows a valve (arrow) lying in the right superior lobe of a 63-year old patient one day following implantation. (**a** p. a., **b** side projection, **c** enlarged view of p. a.). **d, e** show p. a. images from a 70-year old patient taken day 1 **d** and day 8 **e** following valve implantation in the right superior lobe. The centrally lying valves are faintly visible. The post-interventional complication of a major right side pneumothorax was observed, which fully subsided within a week of a drainage being implanted. In **e** atelectasis of the superior lobe is visible with minor traction of the upper mediastinum.

time, since the risk of post-interventional pneumothorax increases due to the hyperinflation of the untreated neighboring lobe among other factors when there is a rapid loss of volume in the target lobe owing to the hyperinflation [23]. While post-interventional pneumothorax following EBV implantation is a frequent complication according to these studies, it has no long-term negative impact on FEV_1 and quality of life [23]. In any case, the relevant frequency of peri-interventional pneumothorax following EBV implantation necessitates post-interventional monitoring, a hospital stay of at least 48 hours [23] and radiological follow-up.

Patients developing complete atelectasis following EBV therapy exhibit significantly better trends in terms of physical activity and spirometrically measurable lung function [24, 25]. In addition, the appearance of complete atelectasis appears to be the main criterion for improved survival following ELVR with EBV [25]. *Hopkinson et al.* ascertained 6-year survival rates following EBV implantation of 100 % and 43 % for subgroups with and without complete atelectasis, respectively [25].

However, there are currently no large randomized controlled studies concerning long-term survival following EBV implantation. The research community is therefore hoping that the "LIVE" study (*a long term follow up investigation of endobronchial valves in emphysema*), which is currently seeking to be the first long-term observation over a period of 5 years, will gather pioneering results.

Irreversible ELVR methods

What all irreversible ELVR methods have in common is that, unlike with EBV, which can be removed bronchoscopically, there is no going back once performed. Additionally, it cannot be absolutely assumed that foreign material introduced will remain anchored in place, given that the lungs move as a result of respiratory excursion. Although rare, complications resulting from material dislocations can be serious, since the pulmonary and bronchial structures can be perforated and even penetrated. Because long-term results for all methods are currently still unavailable, it is not yet possible to make any predictions whatsoever on the carcinogenicity of ELVR therapies.

Endobronchial coils (LVRC, *Lung Volume Reduction Coils*) are introduced bronchoscopically and contract in helical formation upon being released, causing a mechanical contraction of the treated region of the lung. Their principle of application is highly promising, given that they have an immediate effect [26]. It is clearly a disadvantage that implantation of the foreign bodies measuring up to 20 cm long cannot be re-

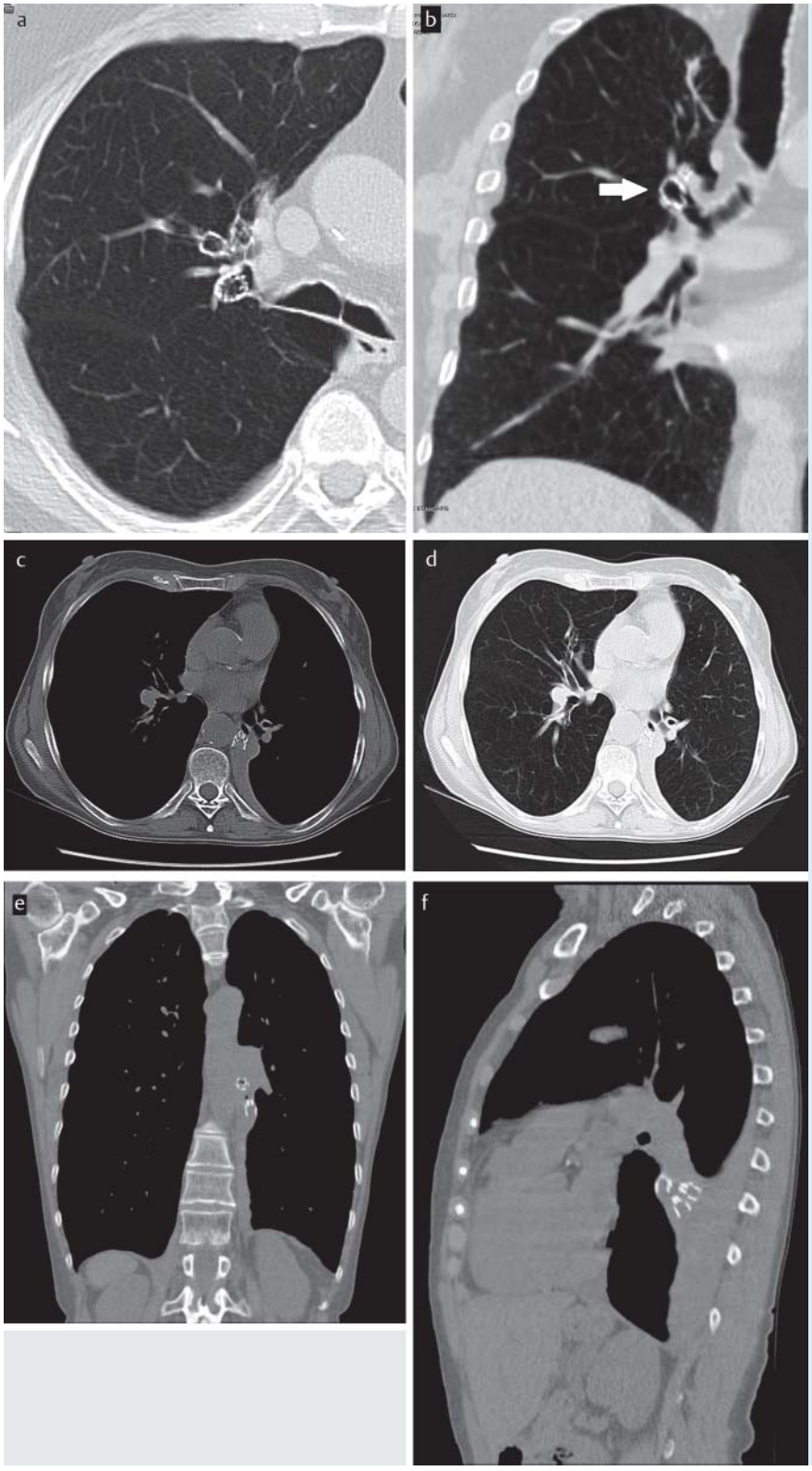

Fig. 3 shows CT images of endobronchial valves. **a, b** are axial **a** and coronal **b** images showing valves lying in the right superior lobe of a 63-year old patient 14 days following implantation. The arrow in **b** points to the valves. The images in **2a–c** and **7a** were taken from the same patient. **c–f** show valves in place with complete atelectasis of the left superior lobe 96 days following implantation in axial (**a** soft tissue window, **b** window), as well as in coronal **c** and sagittal **d** multi-planar reformatting.

garded as a reversible procedure. In addition, their length and shape would appear to make the induction of electrical currents a possibility, even though the manufacturer claims the coils are "MR-compatible". This could at least have an impact on thoracic MRI.

Published in 2013, "RESET" was the first randomized controlled study. While it showed 23 patients following LVRC to have significantly better clinical results than the control group undergoing conservative therapy [27], pneumothorax, infections and COPD exacerbations were observed more frequently. Larger, valid studies are primarily still in progress. Nevertheless, the rate of peri-interventional complications is apparently comparable with that of EBV [28].

While there is less knowledge about therapy with coils than about that with EBV, it constitutes the sole approved ELVR method when ELVR with EBV is not an option due to the presence of "collateral ventilation" (CV, see below). It is possible that LVRC may see increasingly wider user once the results of the currently ongoing, controlled randomized "RENEW" study are available.

Known as **thermoablation** (BTVA, *Bronchoscopic Thermal Vapor Ablation*), the scalding of lung parenchyma using bronchoscopically administered steam serves to in induce an inflammatory response to thereby achieve LVR through the subsequent scarring and fibrotic shrinkage of the treated area of the lung [29]. The onset of effect is therefore delayed compared to the other ELVR procedures, with maximum effect not appearing until after 8 to 12 weeks. In two prospective uncontrolled studies, *Snell et al.* (SGRQ) [30, 31] reported therapeutic success similar to that achieved with EBV, specifically a volume reduction of the target area by up to 48 % and a significant improvement of lung function and quality of life (SGRQ) [30, 31]. A typical post-interventional complication of BTVA is an overreaching inflammation accompanied by flu-like symptoms. However, *Gompelmann et al.* reported highly promising cases of success, particularly in patients with increased post-interventional symptoms, since the severity of the inflammatory reaction appears to correlate with clinical success [29]. A wait-and-see approach is needed for this method still being tested. The currently ongoing “StepUp” study, which will be the first controlled randomized study for this method, could provide further insights

The endobronchial administration of **synthetic polymers** (PLVR, *Polymeric Lung Volume Reduction*) is intended to induce a reduction in lung volume through the mechanical "adhesion“ of the treated areas of the lungs [32]. While these so-called *Sealants* have yielded overall good therapeutic results comparable to those of EBV, severe pneumonia and death were observed more frequently with this therapy. In addition, the majority of patients exhibited peri-interventional flu-like symptoms [32], and the time between the onset of effect and measureable therapeutic success took longer than EBV, requiring 6 – 12 weeks [33].

In the meantime, the active substance AeriSeal (Aeris Therapeutics Inc., USA) is no longer commercially available. It remains to be seen whether this method will be readopted in the future.

Through the use of bronchoscopically implanted, drug-coated **bypass stents** (synonym "bronchial fenestration“, Broncus Technologies, USA) extra-anatomical shunts were made between emphysematous lung areas and the bronchial system, thereby facilitating ventilation and volume reduction of the treated areas of the lungs. Although this method initially showed highly promising clinical improvements, the “EASE” study (*exhale airway stents for emphysema*) documented no long-term clinical success and this method has since been abandoned [34]. The failure of this approach is attributed primarily to the occlusion of the stent resulting from granulation tissue and stent dislocations.

Special imaging methods for pulmonary emphysema

High-resolution computed tomography is the long-established imaging method of choice for detecting pulmonary emphysema [35]. It is significantly more sensitive than conventional radiography, which rarely detects subclinical forms of emphysema [36]. In addition, thin-slice CT usually allows pulmonary emphysema to be clearly differentiated from key differential diagnoses. Unlike pulmonary emphysema, cystic pulmonary diseases such as Langerhans cell histiocytosis or lymphangioleiomyomatosis typically involve hypodense lesions defined by visible walls. The advantages for thoracic diagnostics presented by three-dimensional volumetric datasets that can be reformatted on the spatial planes were already described in the mid-1990 s [37] By enabling the entire lungs to be examined in a single breathing pause for the first time, the growth of multiple detector computed tomography (MDCT) represented a technical breakthrough for thoracic diagnostics.

Considerable amounts of image data are generated with MDCT. Visually comparing multiple examinations is extremely laborious and time-consuming, particularly in the case of diffuse pulmonary diseases such as pulmonary emphysema. Quantitative CT (qCT) should enable the use of time-saving, automated analyses [38]. It can allow the objective and reproducible assessment of clinical follow-up examinations and scientific studies, thereby offering considerable advantages over descriptive image evaluation [39] As MDCT continued to gain prevalence, volumetric datasets with isotropic voxels became increasingly available, which constitute the basis of qCT. Since then, researchers around the world have been studying the automated segmentation of the lower airways [40] and quantitative analysis of the lung parenchyma [4, 38, 41].

With qCT, areas of the lungs with increased air content and consecutively reduced density can be quantified and presented graphically based on the HU values of the voxels. The different techniques of (semi)automatic segmentation and analysis of lung parenchyma have been thoroughly described in multiple studies [38, 41]. The analytic methods common today are mostly threshold value-based, i. e. all voxels below a threshold value are viewed as emphysematous lung parenchyma [42]. The specific threshold value of the emphysema, i. e. that value at which the volumes with lower CT density than emphysematous lung tissue are defined, is primarily set between -910 HU [43] and -950 HU [44]. The so-called *pixel index* is defined as the portion in percent (%) that the voxels below the threshold value constitute of the voxels of the entire pulmonary volume and is also referred to as “emphysema score” when used to emphysema. **Fig. 4** shows a graphic representation of the distribution of the “emphysematous voxels” within the lungs shown in semitransparent view. The 15th percentile of median lung density is considered to be another important parameter (PD15) [42, 45 – 47]. It is ascertained by plotting the density values of all pulmonary voxels in a histogram showing frequency distributions. The advantage it has over *pixel index* (or emphysema score) is that it is affected very little by changes in lung volume, as can be caused by fibrotic processes, for example. Several authors argue that this parameter is thus more suitable for longitudinal studies [46, 47]. According to method employed, however, both

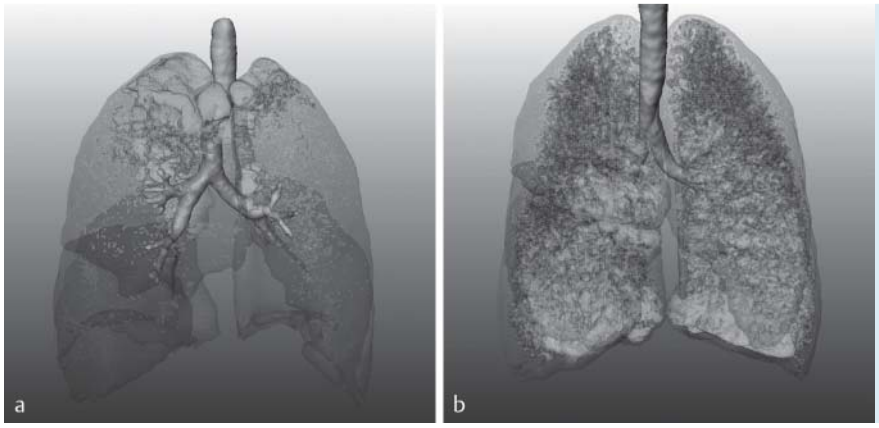

Fig. 4 shows the topographical distribution of emphysema volumes according to volumetry performed with MeVisPULMO 3 D. The areas with radiopacity < –950 HU are highlighted within the lungs shown in semitransparent view. **a** shows heterogeneous, apically focused pulmonary emphysema, while **b** shows homogeneous pulmonary emphysema with discrete central focus. (courtesy of Fraunhofer MEVIS).

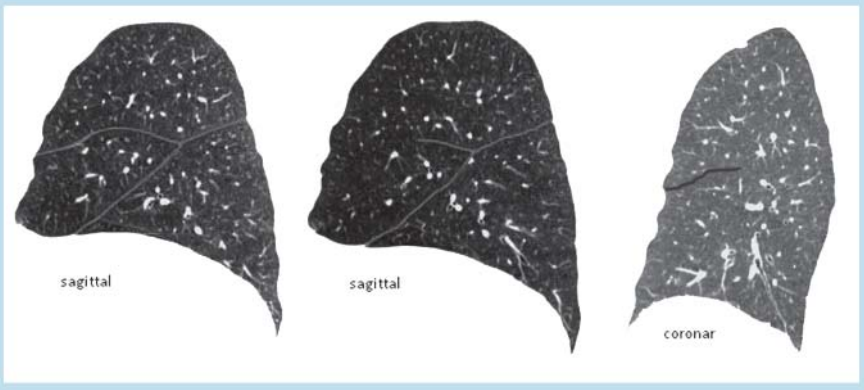

Fig. 5 presents the phenomenon of incomplete lung fissure (IF). The left image shows a sagittal MPR of the right lung with complete lung fissures. The center image shows a further medially reconstructed sagittal slice from the same patient. The large interruption in the minor fissure is clearly visible. Incompleteness is observed most frequently in the minor lung fissure. The right image shows coronal reformatting, allowing the interruption in the fissure to be traced on two planes. The visible courses of the intact lung fissures are highlighted.

parameters depend considerably on examination technique, reconstruction parameters and the inspiration depth of the patient [38]. The introduction of subsequent volume correction while factoring in the particular quantified lung volume can, however, reduce the influence of changing inspiration depths and increase the reproducibility of these parameters [45, 48].

A clinically robust software must function not only on healthy lungs, but must also accurately detect pathological and iatrogenic changes in pulmonary anatomy. Precise segmentation of the tracheobronchial system is helpful, since respiratory air contained in the bronchia can otherwise be falsely interpreted as emphysema volume [49]. For this purpose, most methods employ a *region-growing* procedure starting from an initial point in the trachea, as described by *Selle et al.* [50], and then subtract the volume of the air-filled airways. Other factors influencing qCT are patient age, inspiration depth during examination and technical parameters [51].

Because there were no suitable software solutions in the early 2000 s, the first clinical studies on ELVR employed only a visual evaluation for selecting a suitable target lobe for the minimally invasive therapy. To our knowledge there has not yet been a study definitively proving a clinical advantage of an existing software-supported evaluation. However, the use of lobe-separated volumetry and emphysema analysis in planning therapy prior to ELVR is now technically possible and is seeing increased use in clinical studies.

A lobe-separated volumetry and emphysema analysis can currently be performed only following prior detection of the lobe margins, since the individual lobes are separate from one another and must be analyzed as separate volumes. The first simple methods for automatically detecting and segmenting the lobe margins relied exclusively on the CT density of the individual voxels in the volumetric data sets to detect the contours of fissures directly. However, this is considerably complicated by the expansion, incompleteness or full absence of fissures [41]. Pulmonary diseases can influence the appearance of fissures in a wide variety of ways. In addition, adjacent space occupations, atelectasis and emphysematous areas can cause additional problems [41]. For such reasons, these early programs yielded primarily unsatisfactory results and required time-consuming manual corrections. Modern methods are therefore based on the principle of avoiding any dependency on the existence and visibility of fissures [38]. Current programs use additional anatomical information and are able to automatically detect fissures with acceptable results. *Kuhnigk et al.* are the first to describe a method which, in addition to directly detecting lobe fissures through density values, factors in the distance between the major vessels and the fissures using a blood vessel mask segmented beforehand [41]. The research software "MeVisPULMO 3D" from Fraunhofer MEVIS used at our hospital employs this approach, which factors in the vascular anatomy of each lobe in detecting fissures. The large contrast in density between the blood vessels and the air-filled lung parenchyma means that the automated segmentation of the major vessels is usually sufficient [38]. In their current article examining 96 patients with emphysema, *Van Rikxoort et al.* compare the results of automated segmentation of fissures performed

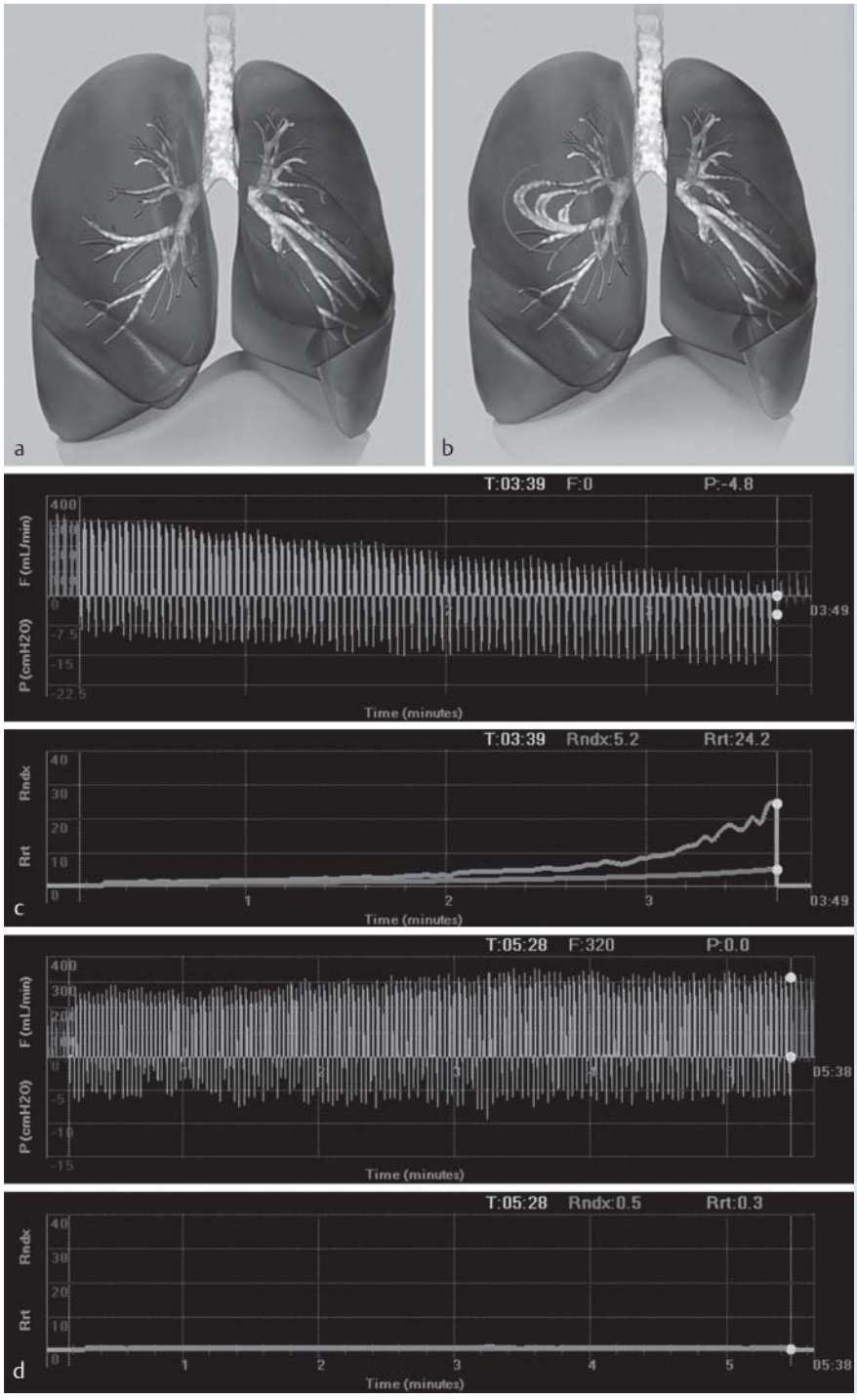

Fig. 6 **a, b** show the phenomenon of collateral ventilation (CV). Normal anatomy without interlobular shunting is illustrated in **a** and the anatomic variant with interlobular shunts in **b**. **c, d** show typical flow curves on the Chartis measurement console. The absence of CV reduces the measurement duration of expiratory flow **c**, while its presence causes a measureable airflow to remain due to the continued flow of air via the functional collateral ventilation **d**. (All images courtesy of Pulmonx Inc.).

by modern software versus a visual *consensus read* performed by three experienced radiologists, likewise finding acceptable agreement [43]. Nevertheless, most published studies employ visual inspections and, if applicable, interactive correction of the contours of the fissures proposed by the software. While this process is time-consuming and the examiner dependency reduces the reproducibility of the analyses, engaging an experienced examiner can salvage examinations that were previously assessed as erroneous due to pathological changes or anatomical variants [38].

Software solutions are currently in development which forego direct detection of the often barely detectable and very often incomplete fissures. For this purpose, a detailed 3-dimensional analysis of the subsegmental anatomy of the tracheobronchial tree is performed and used for locating the lobes. By not being dependent on the completeness of the fissures and the pulmonary vascular anatomy this method looks very promising. Should studies prove its effectiveness, it could render the previous approaches obsolete.

Several major CT equipment manufactures now offer software solutions for CT volumetry and quantification of emphysema. However, an overwhelming number of relevant

clinical studies employ independent programs such as *VIDA* (VIDA Diagnostics Inc., Cupertino, USA), *Myrian* (Intrasens, Paris, France) und *MeVisPULMO 3 D* (Fraunhofer MEVIS, Bremen, Germany). Non-contrast MDCT volumetric datasets with thin primary slice thickness (max. 1.25 mm) taken during inspiratory breath-holding have proven to be suitable equipment parameters for CT volumetry and quantification of emphysema [49]. An automated segmentation of fissures from examinations with slice thicknesses greater than 2 mm cannot be reproducibly performed, since the fissures in the thick slices do not have sufficient contrast density in relation to the lung parenchyma [38]. While a second CT scan taken at maximum expiration can provide important supplemental information, it must not be viewed as obligatory. Areas of the lungs exhibiting *air trapping* in the expiration series [52] are more poorly ventilated due to the bronchial obstruction during expiration. For optimized automated CT volumetry, it is expedient to resort to "soft" kernels given the associated image noise and "hard" kernels for visual analysis of the lobe fissures given the superior image contrast [44]. For CT volumetry, certain examinations must generally be performed using non-contrast methods to prevent, for one, changes in density resulting from the contrast medium containing iodine. Discontinuous CT examinations with incomplete datasets are unsuited for CT volumetry and quantifying emphysema and should no longer be used for these indications.

Current literature is nearly devoid of binding recommendations on the CT radiation dose to be used. In most existing studies, however, examination protocols with high tube voltage (generally 120 kV) were implemented.

When performing evaluation prior to potential LVR, malignant pulmonary tumors that frequently appear in COPD patients must be excluded. Insofar as an evaluation CT reveals suspicious intrapulmonary space occupations, therapy must be postponed and a follow-up examination must be performed after adequate time has elapsed. The obscuring of a malignant tumor by post-interventional dystelectases must be avoided by all means.

Even more difficult is the detection of pathologies of the tracheobronchial system, which are likewise frequently observed in COPD patients and, in many cases, can be more clinically serious than emphysema. For example, bronchopathy with severe tracheobronchial collapse can be easily overlooked in CT or (rigid) bronchoscopic exams. Targeted flexible bronchoscopy or a dynamic 4D-CT scan performed under continuous respiration may confirm a diagnosis of this type [53].

Post-interventional follow-up examinations using medical imaging following LVR are extremely important. Radiographic and CT examinations are able to rule out complications such as pneumothorax, pneumonia and material dislocations in treated patients. Quantitative CT allows changes in volume in the treated area of the lung to be reproducibly and validly monitored, with measureable target lobe volume reduction (TLVR) having become the most important parameter. Improved clinical function, however, is the gold standard for evaluating the effectiveness of a lung volume reduction procedure. In most studies, this clinical success is tested and documented using the 6-minute walk distance test [6MWD], spirometric lung function test parameters (in particular FEV_1) and questionnaires such as the *St. George Respiratory Questionnaire* (SGRQ) or other suitable methods. As of this time, quantifying CT volumetry has only served to provide objectivation of therapy monitoring in studies and does not constitute a clinical standard.

Insofar as EBV have been implanted, it is additionally necessary to monitor their position given the fact that respiratory excursion and heavy coughing can cause the valves to loosen and become dislocated. In this case it is also necessary to thoroughly evaluate the contralateral lung, since it is quite possible for a coughed out valve to be aspirated into the contralateral side. Finally, it is necessary to identify any valves that are correctly located yet displaced by mucus and subsequently verify these findings bronchoscopically, since these valves may not be functioning and may a focus of infection (**Fig. 7b**). If defective valves are identified, the attending pulmonologist must be notified so that a repositioning or replacement can be performed. As another imaging method, perfusion MRI has provided highly promising results in experimental studies. *Ley-Zaporozhan et al.* observed, for example, a "high correlation" between parenchymal destruction detected by CT and reduced perfusion in perfusion MRI [49]. However, this method currently has no relevant significance in routine clinical practice.

While classic ventilation/perfusions-scintigraphy as a nuclear medicine method can detect diffuse abnormalities of peripheral pulmonary vascularization, it is substantially limited in terms of spatial resolution. The considerable improvements achieved in computer-based CT image data a-

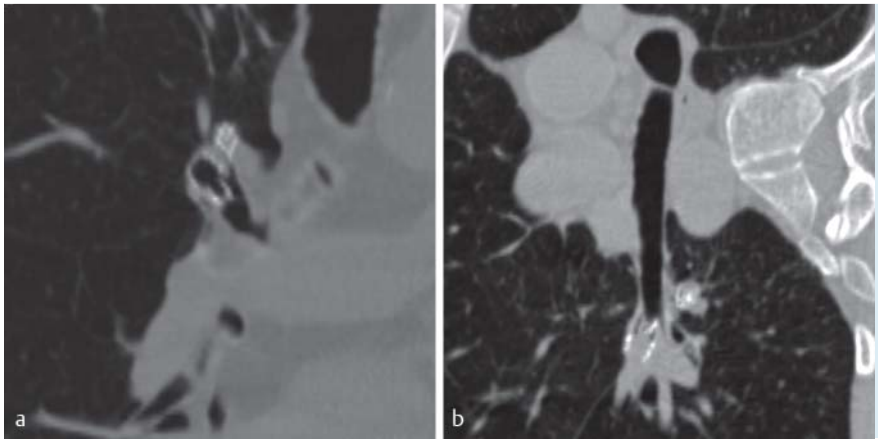

Fig. 7 **a** shows a multiplanar CT reconstruction of a properly resting endobronchial valve in the right superior lobe of a 63-year old patient. **b** shows a valve properly positioned in the right superior lobe of a 59-year old patient, yet displaced by mucus. Because EBV can allow mucus to pass, this image does not necessarily indicate valve dysfunction. In this case, however, bronchoscopy confirmed a loss of function, and the valve was replaced.

nalysis has significantly reduced the relevance of scintigraphy in recent years. As a functional examination, however, scintigraphy continues to be warranted even after the introduction of qCT when searching for heterogeneously distributed and especially hyperventilated areas of the lungs, since it can display very likely local differences an can aid in therapy planning when compared against CT. Today, scintigraphy is used to decide whether LVR is justified. In addition, the wide availability of this examination method is certainly an advantage.

Ventilation/perfusion-SPECT (*V/P single-photon emission computed tomography*) is known as a method for diagnosing pulmonary embolisms, among other conditions. V/P-SPECT was also used in multiple studies to detect and grade pulmonary emphysema [54, 55].

As described above, COPD is diagnosed with the aid of spirometry, which reveals obstructive changes in primarily major and intermediate airways through FEV_1. Because, however, the pathological correlate primarily exhibited by COPD is an obstruction of the minor airways, a better diagnostic method would be desirable. V/P-SPECT can possibly reveal these changes in the minor airways [55]. Individual studies have shown that V/P-SPECT is more sensitive than lung function tests and high-resolution CT [55]. However, the method is still highly experimental, and major comparative studies are required before a definitive assessment can be made regarding its diagnostic accuracy.

Collateral ventilation – the challenge for pulmonologists and radiologists

Collateral ventilation (CV) is a term for describing the phenomenon of interlobular shunting of airways, which can result in functional fusion of neighboring lobes [56, 57]. Regarded as microanatomical correlates of collateral ventilation, Kohn's pores and Lambert's canals can communicate both within a lobe as well as between adjacent lobes [44]. First described in 1893, Kohn's pores are interalveolar pores that allow the passage of air, liquid and cells [58]. Described in 1955, Lambert's canals constitute epithelially lined bronchioloalveolar connections [58]. Both structures are too small to appear visible on CT, their existence being confirmed through electron microscopy.

While accessory collateral ventilation has an insignificant effect on the respiratory physiology of healthy lungs, different mechanisms promote the formation of collateral ventilation in lungs damaged through emphysema [59]. *Higuchi et al.* accordingly demonstrated that up to 66 % of all patients with high-grade pulmonary emphysema exhibit functionally effective CV [25]. The pathophysiological mechanism of increased appearance of CV in emphysema patients is not yet understood. However, the formation of additional shunt connections resulting from the mechanical tearing of alveolar walls is being discussed as one possibility.

The occurrence of *incomplete fissures* (IF) was first described in the 1940 s [60]. In recent years, numerous studies concerning modern ELVR methods have led to a better functional understanding of this frequent anatomic variant [43]. *Aziz et al.* conducted a visual CT analysis of the completeness of fissures in 622 healthy patients, finding IF in 43 % of left fissures, 48 % of major right fissures and 63 % of minor right fissures [61]. Comparable studies involving smaller populations have confirmed the normal incompleteness of the minor right fissure. IF therefore is not the exception and cannot be regarded as pathological. The frequency of IF in emphysema patients is approximately the same as that of the healthy population. *Van Rikxoort et al.* ascertained, for example using automated CT analysis of the fissures, the respective frequencies of IF in 96 emphysema patients to be 33 % (left fissure), 51 % (major right fissure) and 85 % (minor right fissure) [43]. IF is present if CT shows < 90 % of the fissure to be traceably intact in a spatial plane [62].

However, not all patients with IF have CV. Frequently, CV is incorrectly used synonymously with IF [25, 63].

The highly publicized 2010 "VENT" study was the first randomized controlled study on occlusive valves. In terms of its primary goal, the study can thoroughly be deemed a failure, since it was able to only demonstrate a modest clinical improvement short of expectations in FEV_1 and quality of life in 220 patients treated with EBV. A visual evaluation of pulmonary fissures using pre-interventional CT exams was conducted in a retrospective subgroup analysis, which recorded clearly better clinical results in patients with complete fissures and heterogeneous, lobe-focused pulmonary emphysema [19]. A complete fissure therefore appears to be a predictor of absent or only minor CV. Published in 2012, the "EuroVENT" study yielded similar results, albeit with a somewhat smaller number of cases, for clinical outcome and peri-interventional complications following ELVR study as the "VENT" study [62]. For example, an average improvement in FEV_1 by 26 % was observed in patients with complete fissures and correctly positioned valves fully occluding the bronchus [62]. The EuroVENT study also proved that EBV can be clinically successful even in patients with homogeneously distributed pulmonary emphysema provided that complete fissures are present according to CT analysis [62].

The criteria for *heterogeneous* pulmonary emphysema vary in the literature and are not standardized In most studies a difference in percentage-based emphysema score between neighboring lobes of at least 10 % [44] to 15 % [19] is defined. However, in clinical practice the heterogeneity of the pulmonary emphysema is established not with exhaustive quantitative CT analysis, but rather on the basis of the reviewer's assessment. Functional interlobular connections within the bronchial system jeopardize the therapeutic success of ELVR with EBV, therefore necessitating that CV be excluded prior to valve implantation [19]. Only in this way can the right patients likely to exhibit successful results be selected [44]. Careful therapy planning prior to EBV implantation is a must and cannot always be ensured outside specialized centers.

Bronchoscopic function testing is an option for preoperative evaluation of CV. Employing a bronchoscopic work canal, the *Chartis* measurement device from *Pulmonx* (Redwood City, CA, USA) allows brief balloon occlusion of a bronchus and measurement of airflow via a canal in the balloon catheter [44]. If CV is present, a measurable airflow will remain as a result of air continuing to flow via the functional collateral ventilation. The measurement duration of expiratory airflow is reduced in the absence of CV [64]. **Fig. 6** shows the phenomenon of CV using schematic drawings and typical flow curves on the *Chartis* measurement console.

method	availability	reversibility	heterogeneous pulmonary emphysema	homogeneous pulmonary emphysema	contraindications
lung volume reduction surgery (LVRS)	yes	no	yes	only under strict patient selection	"terminal" COPD
endobronchial valves (EBV)	yes	yes	yes	only if negative for CV	collateral ventilation
coils (LVRC)	yes	incompletely	yes	yes	(possible bullous emphysema)
thermoablation (BTVA)	yes	no	yes	yes	none
sealants (PLVR)	no	no	yes	yes	obsolete
stents	no	no	yes	yes	obsolete

Table 1 provides an overview of the LVR methods described in the article, for which emphysema subtypes they can be employed and which contraindications exist.

An important advantage of the *Chartis* system is that it enables direct measurement of the CV, which can be performed only by the bronchoscope operator. In addition, this method does not involve radiation exposure, which is unavoidable with CT-based fissure analysis. Nevertheless, *Chartis* measurements can be considerably complicated by patient-related interference factors such as coughing and bearing down, incomplete balloon occlusion, excessive mucus formation with blockage of the measurement device in the catheter tip and complicated anatomy [65]. Unlike CT-based fissure analysis, it is additionally an invasive method that is highly dependent on the experience of the person performing the examination.

In a study involving 25 patients, *Reymond et al.* compared visual assessment of the completeness of fissures performed by two experienced radiologists with *Chartis* measurements, finding 73 % concordance between both methods [44], which suggests a close connection between the CT morphology of fissures and functional measurements. Despite this, the visual examination of fissures, while demonstrating good sensitivity (95 %) and good NPV (88 %) yielded unsatisfactory results for specificity (44 %) and PPV (69 %) [44]. According to visual examination, 65 – 92 % (depending on lobe) of the fissure were incomplete, while only 57 % of the lobes tested with *Chartis* were clinically positive for CV. The problem of low specificity is due to the fact that many CV-negative patients exhibit IF on CT [44]. In any case, 95 % of the CV-positive patients also exhibited a fissure defect on CT [44]. Evaluation with the automated methods already described is more convenient, less dependent on person performing the examination and less time-consuming than visual analysis of fissure completeness [38]. However, there have not yet been sufficiently large studies to allow a comparison with *Chartis* measurements. In an autopsy study, the fissure completeness was predicted from CT datasets with acceptable sensitivity and specificity [57]. *Herth et al.* studied whether *Chartis* measurements can achieve comparable predictive capability for CV as CT-based fissure analysis [64]. In the *"Chartis"* study, 80 patients were evaluated using both methods prior to EBV implantation. In 88 % of patients, the predicted volume reduction of ≥ 350 ml was achieved in the target lobe within 30 days following the intervention when *Chartis*- and CT-analysis concurred, i. e. ascertained complete fissures and were negative for CV. None of the patients testing positive for CV beforehand achieved this threshold value. With a positive predictor (PPV) of 71 % and a negative predictor (NPV) of 83 %, evaluation with *Chartis* yielded an overall predictive accuracy of 75 % [64] and thus highly promising results. Patients testing negative for CV additionally achieved a significantly higher improvement in FEV_1 than the group testing positive for CV [64]. In a current retrospective analysis of 69 patients from the *"Chartis"* study, *Gompelmann et al.* likewise ascertained a comparable predictive accuracy between *Chartis* and a CT-based fissure analysis [66]. *Chartis* can accordingly be viewed as a safe and effective method for predicting therapeutic success following ELVR with EBV [64].

Smaller uncontrolled studies suggest that complete atelectasis can be achieved in up to 90 % of cases following *Chartis* evaluation [65]. However, there are still no clinical parameters that can aid in reliably predicting whether patients will develop a relevant volume reduction in the target lobe measureable as TLVR following EBV treatment [67].

In concept, lung volume reduction surgery and coils are independent of CV. The effects of CV on the clinical results of thermoablation [68] and sealants [69] is not significant (see ▶ **Table 1**).

Concluding statements

The goal of lung volume reduction for the treatment of emphysema is to improve breathing mechanics by reducing chronically hyperinflated, dysfunctional areas of the lungs. In addition to surgical partial lung resection (LVRS), three different minimally invasive, bronchoscopically assisted techniques are currently available.

Of all ELVR methods, occlusive endobronchial valves are currently the most scientifically studied and present a therapy option and alternative to surgical procedures for patients with heterogeneously distributed pulmonary emphysema and negative collateral ventilation (CV). In the process of critical scientific examination of these novel therapy methods, several experts justifiably point out that, given the continued lack of any long-term studies and the relevant complication rates, ELVR with EBV is still an experimental therapy method outside evidence-based guidelines, and therefore demands an extremely critical indication procedure and should not be employed lightly. Despite the state of research still being insufficient in many regards, particularly concerning post-interventional long-term survival, a relatively high number of patients are currently being treated with ELVR techniques in Germany. This is due to the fact that because the (compulsory) health insurance companies assume the costs of selected ELVR therapies (EBV and LVRC), therapy is frequently offered and deman-

Table 2 provides a summary of this survey article.

1	Lung volume reduction (LVR) is a treatment option for advanced pulmonary emphysema. The volume of dysfunctional areas of the lungs is reduced in an attempt to decrease hyperinflation of the lung parenchyma, improve breathing mechanics and ultimately achieve a measureable clinical improvement.
2	In addition to lung volume reduction surgery (LVRS) with endobronchial valves, coils and thermoablation, three other minimally invasive, endoscopically assisted methods (ELVR) are currently available. With all LVR methods relevant peri-interventional complications such as, for example, pneumothorax, hemoptysis and exacerbation of COPD are observed.
3	Endobronchial valve implantation (EBV) has special significance, since it is the only method that it is fully reversible and is the most scientifically studied of the minimally invasive ELVR methods. However, EBV is the only method in which the phenomenon of "collateral ventilation" (CV) is an issue, making patient selection especially important. Pre-interventional evaluation of this phenomenon through analysis of pulmonary fissures on the basis of CT scans and/or bronchoscopic function testing is therefore standard in studies and at specialized centers. Valve implantation should not be performed without these prior evaluations, as clinical success may otherwise be jeopardized.
4	ELVR methods have still not been definitively researched and have hence yielded little evidence. Despite this, however, EBV are already seeing frequent use, driven by the benefits policies of health insurance companies. Many experts find fault with an all too "uncritical" use of ELVR therapies, since the clinical results of procedures performed outside of scientific studies and specialized centers frequently fall short of expectations.
5	The primary role of radiologists is to support thoracic surgeons and interventional pulmonologists in selecting the target area best suited for LVR. In this endeavor, lobe-by-lobe quantitative analysis of CT scans (qCT) can be superior to purely visual image analysis. However, this is not yet widely used. Prior to EBV implantation, a CT analysis of pulmonary fissures is usually performed visually. Time-saving automated computerized systems have already shown highly promising results in studies, however. Following intervention, detecting complications is of primary importance. Quantification of the change in volume in LVR target lobes can additionally be performed, usually as part of studies. The practical importance of these analyses should not be overvalued, since therapeutic success following LVR is evaluated based exclusively on changes in clinical parameters.

ded outside the scope of studies and outside of specialized centers [6, 70]. Many experts thus feel that ELVR is employed too "liberally" today. This results in the clinical improvements lagging behind the results published in studies, due primarily to insufficiently critical patient selection and the use of technical *know-how* that is in need of updating.

Since the VENT study, it is known that endoscopic lung volume reduction (ELVR) with EBV is not indicated for patients testing positive for CV. Alternatives to ELVR with EBV would be lung volume reduction surgery (LVRS) and various irreversible, non-blocking ELVR methods. Because of their mechanisms of action, these therapies can be performed regardless of CV and can be used if the presence of CV constitutes the key contraindication for ELVR with EBV. In contrast to LVRS, novel irreversible ELVR methods with *sealants,* thermoablation and coils have still not been sufficiently researched, however, and should thus for the time being be used only in the context of clinical studies until satisfactory long-term results become available.

Quantitative computed tomography (qCT) is the method of choice for evaluating pulmonary emphysema lobe-by-lobe and recommending the optimal target lobes for ELVR to the interventional pulmonologist [44]. Aside from the fact that it is not yet technologically possible, a quantified evaluation of emphysema on the segment level is not necessary, since EBV always requires that all segments of a pulmonary lobe be closed. In addition, the presence of CV must be evaluated prior to the implantation of endobronchial valves. This can be performed either by means of bronchoscopic function testing with the *Chartis* system or through visual analysis of the completeness of pulmonary fissures in pre-interventional CT exams. Both methods have proven themselves independently of one another in multiple studies and, in the few comparative studies, have yielded equivalent results in terms of predicting the success of therapy. An automated evaluation of the completeness of fissures, which would save both time and resources, would be desirable. Currently, however, this method does not function robustly and is used only in an experimental capacity.

Medical imaging following LVR is extremely important. Radiographic and CT examinations are usually able to reliably identify immediately peri-interventional complications such as pneumothorax, pneumonia and material dislocations. Another round of imaging would appear to be expedient following an appropriate interval for each individual method and as soon as the onset of therapy can be assumed. CT can detect late complications typical for the procedures, such as air fistulae and suture insufficiency with LVRS, ventilation dislocation with EBV, material rupture with LVRC and prolonged inflammatory reactions with BTVA. Quantitative CT facilitates objectivation of the volume reduction in the target lobe, thus allowing comparison with the development of clinical parameters. However, this is currently used only in studies and at specialized centers and is not (yet) part of routine clinical practice.

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