Interventional Pulmonology

Respiration

Respiration 2016;91:241–250
DOI: 10.1159/000444090

Received: December 7, 2015
Accepted after revision: January 16, 2016
Published online: February 25, 2016

Endoscopic Lung Volume Reduction: An Expert Panel Recommendation

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Key Words
Chronic obstructive pulmonary disease · Emphysema · Bronchoscopy · Lung volume reduction · Expert statement

Abstract
Chronic obstructive pulmonary disease (COPD) is a progressive condition comprising a constellation of disorders from chronic bronchitis, airflow obstruction through to emphysema. The global burden of COPD is estimated at more than 6% of the population. The standard of care is based on a combination of smoking cessation, immunization, pharmacological treatments and pulmonary rehabilitation. However, the more advanced stages of COPD are challenging to manage. In this situation, our current standards of care do not adequately control patient symptoms nor halt the progressive decline. For the emphysema phenotype, lung volume reduction surgery has shown a beneficial effect in selected patients but is counterbalanced by the morbidity experienced by some patients. Bronchoscopic volume reduction technologies have been developed to improve the clinical situation of emphysema patients. This expert statement provides broad guidance regarding patient selection and the current position of the available techniques for patients with advanced emphysema.

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic disease of the lungs. The classical symptoms of COPD are shortness of breath, excessive production of sputum, and chronic cough [1]. COPD is progressive and ultimately a life-threatening disorder. Treatment can slow its progression, but it cannot be cured. The emphysema subgroup is characterized by progressive alveolar damage and loss of alveolar structure, particularly alveolar tetherings [2]. The net effect is reduced surface area for gas exchange but also pressure-dependent airway collapse. The physiology is characterized by both static and dynamic hyperinflation [3].

Accurately estimating the prevalence of COPD is difficult due to widely varying diagnostic criteria, varying methods and different reporting rates, e.g. from patients versus diagnosticians. These and other factors may lead to widespread underreporting of COPD [4].

In a systematic review and meta-analysis, the pooled prevalence estimate for COPD was 7.6%, including studies reporting combined chronic bronchitis and emphysema [5]. The burden of the disease results in an estimated economic cost of USD 2.1 trillion for 2010, and USD 4.8 trillion for 2030 [6].

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Table 1. Baseline characteristics of the endoscopic lung volume reduction trials compared to the initial NETT trial inclusion criteria

Inclusion criteria	NETT	EBV/VENT	IBV	Coils	Bio-LVR	BTVA
Age, years	40–74	63	65	60	64	63
Emphysema location	All	UL/LL	UL/LL	UL/LL	UL	UL
FEV_1, % predicted	20–45	30	31	29	31	31
RV, % predicted	>150	216	221	238	238	237
PaO_2, mm Hg	>45	69	68	64	65	64
$PaCO_2$, mm Hg	<50	41	41	42	41	40
6MWT distance, m	>140	333	337	306	293	300

Bio-LVR = Biological lung volume reduction (Aeriseal).

Risk factors for COPD are tobacco smoking and occupational or environmental exposure to particulates or harmful gases. Smoking cessation may be accomplished through patient education and counselling. The medical standard of care for treatment of COPD consists of treatment with one or more bronchodilators, including B_2 agonists and anticholinergic agents. All bronchodilator drugs commonly used to treat stable COPD have been shown to improve symptoms and to reduce the number and duration of exacerbations [7].

COPD is a progressive disease with around half of the severe-stage patients developing severe hyperinflation [8]. In 1957, Brantigan and Mueller [9] performed the first lung volume reduction surgery (LVRS) procedure, in which tissue from one or both lungs is resected in order to treat the physiological consequences of emphysema. Despite the good long-term data in highly selected patients, LVRS is associated with significant mortality and morbidity, especially in high-risk patients.

Despite the demonstrated efficacy in the National Emphysema Treatment Trial (NETT) more than 10 years ago, LVRS is extremely scarcely used. Illustrative of this is the Medicare reported number of 93, 65 and 42 LVRS procedures performed in the USA in the years 2011–2013 [10]. Also the number of post-NETT LVRS published original scientific trial papers is very scarce. A number of new technical changes have been proposed to reduce adverse events, but hardly investigated and only reported as case series and a single RCT. Two interesting techniques, which should be further investigated, involve unilateral lobe resection by video-assisted thoracoscopic surgery [11] and nonresectional LVRS, which entails plication of the most severely emphysematous target areas [12].

LVRS candidates are biological lung volume reduction candidates and vice versa (table 1), and the dramatic improvements observed with LVRS in well-selected patients, combined with the need for less invasive options for surgically unfit emphysema patients have stimulated the development of endoscopic lung volume reduction [13, 14].

Patient Selection

Potential evaluable patients for advanced emphysema treatments are those who are already receiving the best medical treatment, i.e. optimal pharmacological therapy mostly with bronchodilators, inhaled corticosteroids, and sometimes maintenance systemic therapies. Patients should also have completed pulmonary rehabilitation and/or are participating in a structured physical therapy program, and have definitely stopped smoking. The key evaluations include a full medical assessment, lung function measurements, CT scan of the thorax, and the 6-minute walk test (6MWT). Based on the available data, patients with severe airflow obstruction [i.e. GOLD stage 3/4 (C/D), FEV_1 20–45%], hyperinflation (RV >175% or RV/TLC >0.58), and a reduced 6MWT (100–500 m) may be considered for lung volume reduction therapies. Patients with severe pulmonary hypertension (right ventricular systolic pressure measured by echocardiography >50 mm Hg) and significant comorbidities, which cannot be corrected, should be excluded (table 2).

Radiological Assessment

Standardized CT scans are required to characterize the emphysema, evaluate the distribution of the emphysema destruction and determine the integrity of the lobar

Table 2. Main inclusion and exclusion criteria for lung volume reduction therapies

Inclusion	Exclusion
COPD – emphysema phenotype	Clinically significant bronchiectasis
FEV_1 20–45% of predicted	Previous lung surgery: lobectomy, pneumonectomy, lung transplantation
RV >175% of predicted	Severe hypercapnia ($PaCO_2$ >8 kPa or 60 mm Hg) and/or hypoxia (PaO_2 <6.0 kPa or 45 mm Hg) both at room air at sea level
RV/TLC >58%	DLCO <20% of predicted
Optimal medical treatment	Significant pulmonary hypertension: right ventricular systolic pressure >50 mm Hg on echocardiography
Nonsmoking	Congestive heart failure (left ventricular ejection fraction <40%)
Postrehabilitation	Significant comorbidities significantly affecting performance and survival
Symptomatic (mMRC >1)	Maintenance anticoagulation: coumarines, low-molecular-weight heparin, clopidrogel or similar antiplatet agents, dabigatran or similar
6MWT distance 100–500 m	

fissures. The CT protocol should be a standardized noncontrast volume acquisition on a multidetector scanner platform with thin (0.6–1.25 mm) series with some overlap. The primary assessment should also ensure the absence of significant comorbidity or abnormalities that require further assessment. If there are unexpected findings like bronchiectasis, pulmonary nodules, suspected lung cancer, interstitial fibrosis or severe tracheobronchomalacia, then the patients should be evaluated and treated based on the underlying disease. It would be inappropriate to consider them for endoscopic lung volume reduction.

The pattern of emphysema observed on the CT scan can be described as follows:

- centrilobular emphysema (most common)
- panlobular emphysema
- paraseptal emphysema
- localized emphysema.

The centrilobular pattern affects the proximal respiratory bronchioles which are seen as focal lucencies measuring from hardly visible defects up to 10–20 mm in diameter, located centrally within the secondary pulmonary lobule. The changes often involve the upper lobes or the apical segments of the lower lobes. The panlobular form involves the whole of the secondary pulmonary lobule, or even bigger defects, and often affects the lower lobes and tends to lead to more homogeneous involvement. Paraseptal emphysema affects the peripheral parts of the secondary pulmonary lobule. It is typically adjacent to the pleural surfaces and leads to the formation of subpleural bullae, with most often very well preserved more central lung tissue. Focal areas of destruction of the alveolar tissue with preservation of other areas are best described as localized emphysema.

Emphysema quantification on CT is usually expressed as the proportion of pixels of <−910 or −950 Hounsfield units (HU) [15]. The −910 HU density threshold is commonly used for thick-slice (>3 mm) CT scans. This threshold yielded the best correlation between emphysema, as determined from resected lung tissue and 10-mm-thick slice CT measurements [16]. With the advent of multislice scanners, also using volumetric reconstructions, the density thresholds for emphysema for different scan settings have been reinvestigated [17]. The strongest correlation between the pathology of macroscopic and microscopic emphysema and CT measurements has been reported at a threshold of −950 HU in 1-mm noncontrast chest CT scans [18, 19]. Several density thresholds have since been proposed for emphysema quantification, but for thin-slice volumetric chest CT scans, −950 HU is nowadays the most commonly used threshold.

Using emphysema quantification scores, a relative lobar difference of this measure is regarded as heterogeneity. This can be done by simple visual analysis, but more accurate results are produced using software systems. Heterogeneity is the relative or percentage difference in the emphysema scores between ipsilateral lobes. To date, no clear definition exists for heterogeneity. In most trials reported, a >25% difference in the proportion of pixels of <−910 HU or a >15% difference in the proportion of pixels of <−950 HU has been used.

Finally, fissure integrity should be assessed, since this will guide the choice of treatment, and is defined as the completeness of the fissure [more than 85% of the fissure present on thin-slice high-resolution computed tomography (HRCT)] on all three axes (sagittal, axial and coronal view). Once again, this is possible visually with large interobserver variability, but more sophisticated software

analysis produces more consistent results [20]. Based on the opinion of the expert panel, such an option should be used if available.

The Technologies

For all technologies described in this paper, see also table 3.

Endobronchial Valves

Used first in 2002 [21], the one-way endobronchial valve (EBV) therapy remains the best studied until now. Valve treatment is targeted to the most emphysematous destroyed lung lobe, which will need to be completely occluded by the valves. The one-way EBVs are placed bronchoscopically to occlude the emphysematous lobe. The goal is to create an atelectasis of the region of the lung similar to that achieved by LVRS, although with valves. The valves allow the air to be expelled during expiration but not to enter the lobe during inspiration, thus facilitating the creation of a full lobar atelectasis. At the moment, two different valves are commercially available, the EBV (Zephyr, Pulmonx Inc., Neuchâtel, Switzerland) and the intrabronchial valves (IBV; Olympus, Tokyo, Japan).

For the EBV systems, three larger RCTs have been published. Two of them were performed by the VENT study group [22, 23]. The randomized trial with the IBV met its clinical end-point, but there was no difference in quality of life or pulmonary function parameters [24]. The treatment strategy was bilateral incomplete lobar exclusion. The trials with the Zephyr valves demonstrated that the treated group significantly improves compared to an untreated control group. However, the results were not clinically meaningful. A post hoc analysis revealed that patients with a complete interlobar fissure on the HRCT scan experienced the best outcome following EBV implantation. A complete fissure (in this post hoc analysis defined as >90% completeness of the fissure) between target and adjacent lobes on HRCT was used as an indirect surrogate for no or negligible interlobar collateral ventilation [25].

In a recently published trial by Davey et al. [26], this hypothesis was confirmed in a randomized, sham-controlled trial. In this study, unilateral lobar occlusion with EBV in patients with heterogeneous emphysema and intact interlobar fissures assessed on CT produces significant improvements in lung function as well as improvements in the quality of life. Therefore, a pretreatment fissure analysis must be performed, and patients with an incomplete fissure should not be considered for treatment with valves. The exact completeness of the lobar fissure necessary for an effective treatment is not well known. But there is a strong correlation between fissure completeness and valve treatment effect as measured by the occurrence of the desired lobar atelectasis, or by the measurement of actual collateral ventilation. The current data indicate that if the interlobar fissure between the treatment target lobe and adjacent lobe is less than 85% intact, proceeding to valve treatment is not useful because of the high likelihood of present collateral flow. On the other hand, if the fissure is between 95 and 100% complete on CT, there will be a very low occurrence of significant collateral flow [27].

To assess interlobar collateral flow, dedicated endoscopic measurement of the collateral flow is possible with the Chartis Pulmonary Assessment system (Pulmonx). Whether a patient is a candidate can be decided using bronchoscopy [28]. In a multicenter European study, it was shown that the fissure analysis and the endoscopic measurement have a high correlation [29].

Recently, Klooster [30] published the first results of STELVIO, an RCT, in which the best responder criteria to EBV treatment were evaluated using the measurement with the Chartis system as the primary treatment assessment tool. In this trial, 84 patients with >90% complete fissures on CT were recruited, of whom 13 still showed presence of collateral flow. Intention-to-treat analyses at 6 months showed significant ($p < 0.01$) between-group differences in favor of the EBV group which showed a change of FEV_1 +140 ml (95% CI; 55–225), FVC 347 ml (95% CI; 107–588) and 6MWT distance +74 m (95% CI; 47–100), with an overall clinical significant responder rate to the treatment of 75%.

Combing CT analysis with fissure assessment is even more important since several studies showed the low correlations between the fissure analyses by various – even expert – readers, except for bigger gaps of more than 30% [20]. To illustrate this: in the study by Davey et al. [26], there were 4 patients who were found to have collateral ventilation as measured by Chartis despite an intact fissure, and these patients had no clinical improvement and did not develop atelectasis.

When taking all these trials together, evidence is accumulating that with EBV treatment real personalized medicine for the treatment of patients with severe emphysema is possible, with even as high as a 75% responder rate to treatment when using a combined approach for recruiting potential candidates: assessment of fissure integrity to

Table 3. Summary of trial design, number of patients, follow-up duration and the main efficacy parameters (FEV_1, RV, 6MWT distance and SGRQ) for the endoscopic lung volume reduction trials published

Device/first author, year [Ref.]	Trial design	Patients treated, n	Follow-up duration	ΔFEV_1	ΔRV	Δ6MWT distance	ΔSGRQ, total score
EBV							
Davey, 2015 [26]	Double-blind sham-controlled RCT Single center	25	3 months	0.06 L (0.02–0.38) 8.77% (2.27–35.85)	–0.26 liters (–1.07 to –0.16) –6.58% (–18.60 to 2.94)	25 (7–64)	–4.40 (–16.93 to 6.76)
Klooster, 2015 [30]	Prospective RCT Single center	34	6 months	216 (128–304) ml		92 (64–120) m	–17.4 (–24.8 to –10.0)
Park, 2015 [53]	Prospective open-label single-arm trial	43	3 months (n = 35)	0.68±0.26 to 0.89±0.37 liters	4.98±1.15 to 3.91±1.15 liters	233.5±114.8 to 283.7±121.6 m	65.59±13.07 to 55.70±13.79
	Single center		6 months (n = 27)	0.68±0.26 to 0.92±0.40 liters	4.98±1.15 to 3.67±0.95 liters	233.5±114.8 to 299.6±87.5 m	65.59±13.07 to 53.76±11.40
Herth, 2013 [29]	Nonrandomized prospective trial Multicenter	51 (CV negative patients)	30 days	0.14±0.20 liters 16±22%	4.49±1.22	24±57	–10±13
Herth, 2012 [23]	Prospective RCT Multicenter	44 (intact fissures)	6 months 12 months	16±21% 15±29%		11±34% 13±35%	–6±15 0±15
Sciurba, 2010 [22]	Prospective RCT	220	6 months	4.3% (95% CI: 1.4–7.2) 34.5 ml (10.8–58.3)		2.5% (95% CI: –1.1 to 6.1) 9.3 m (95% CI: –0.5 to 19.1)	–2.8 (–4.7 to –1.0)
IBV							
Szlubowska, 2015 [54]	Prospective observational study Single center	20	3 months				–12.8±11.9
Ninane, 2012 [24]	Single-blinded sham-controlled RCT Multicenter	37	3 months 6 months	0.99±0.35 to 0.90±0.34 liters	4.65±1.30 to 4.86±1.35 liters	337±106 to 344±18 m	–4.3±16.2 –10.9±18.2
Eberhardt, 2012 [36]	RCT Single center	11 (unilateral) 11 (bilateral)	30 days 30 days	267±154 ml 13±140 ml	–546±1307 ml 61± 990 ml	47.8±55.7 m –25.0±81.5 m	–12.2±13.4 –0.3±9.8
Sterman, 2010 [55]	Prospective, open enrollment, consecutive case series Multicenter	91	6 months 12 months	0.87±0.25 to 0.83±0.29 0.87±0.25 to 0.85±0.33	4.74±1.06 to 4.89±1.17 4.74±1.06 to 4.71±1.27	338±95 to 351±102 338±95 to 358±92	–8.2±16.2 –9.5±14.4
Coil							
Gulsen, 2015 [56]	Retrospective analysis Single center	40	6 months	+0.15 liters (+24.7%)	–0.82 liters (–14.5%)	+ 48 m	–10.4
Deslee, 2015 [41]	Prospective randomized controlled superiority trial Multicenter	50	1 year			36% improvement ≥54 m	
Kontogianni, 2014 [57]	Retrospective analysis Single center	26	90 days 180 days	0.10±0.13 liters 0.04±0.12 liters	–0.6 liters –0.42 liters	47±54 m 32±60 m	–7 –6
Klooster, 2014 [42]	Prospective, open-label, cohort trial Single center	10	3–4 months	16.6% (–16 to 55)	–0.79 liters (–1.20 to 0.04)	42 m (15±141)	–11 (–25±6)
Deslee, 2014 [43]	Prospective open-label feasibility study Multicenter	60	6 months 12 months	15.4±26.7% 16.0±35.5%	–11.3±15.3% –13.8±12.7%	29.7±74.1 m 51.4±76.1 m	–12.1±12.9 –11.1±13.3
Shah, 2013 [40]	Prospective RCT Multicenter	23	90 days	14.2% (6.8–21.6)	–0.51 liters (–0.73 to –0.30)	51.2 m (27.7–74.7)	–8.1 (–13.8 to 2.4)
Slebos, 2012 [39]	Prospective cohort pilot study Single center	16	3 months 6 months	19.9±20.0% 14.9±17%	–11.1±9.9% –11.4±9%	62.2±76.6 m 84.4±73.4 m	–12.6±10.8 –14.9±12.1

Table 3 (continued)

Device/first author, year [Ref.]	Trial design	Patients treated, n	Follow-up duration	ΔFEV_1	ΔRV	Δ6MWT distance	ΔSGRQ, total score
Vapor							
Herth, 2016 [58]	RCT Multicenter	44	6 months	+13.1% predicted		+31 m	–11.1
Herth, 2012 [45]	Two open-label, single-arm studies	44	6 months	141±166 ml	–406 ±714 ml	46.5±67.1 m	–14.0±15.1
	Multicenter		12 months	86±174 ml	–303 ±776 ml	18.5±63.7 m	–11.0±14.0
Snell, 2012 [44]	Pilot study	11	6 months	0.77–0.79 (0.49–1.18)	4.16 (4.00–5.85) to 4.13 (2.99–5.77)	359 (233–495) to 362 (210–527)	64.4 (37–84) to 49.1 (32–64)
AeriSeal							
Come, 2015 [51]	RCT	59	3 months (n = 34)	110 ml (18–211 ml)		not collected	–11 (–18 to –1)
	Multicenter		6 months (n = 21)	100 ml (0–370 ml)		31.0 m (0–41.3 m)	–12 (–22 to –5)
Kramer, 2012 [50]	Single-arm, prospective study	20	6 months	335±438 ml	–485±981 ml	11.8±57.5 m	–8.0±17.2
	Multicenter		12 months	278±425 ml	–864±948 ml	8.6±65.2 m	–7.0±15.8
Herth, 2011 [49]	Pilot study, noncontrolled, open-label	21	21 weeks	0.070±0.193 liters		35.6±66.7 m	–7.1±14.2
	Multicenter		24 weeks	0.105±0.201 liters		24.6±58.9 m	–7.5±14.4

preselect patients, and confirm absence of collateral flow with Chartis.

The major complications after a valve placement are COPD exacerbations, hemoptysis, valve migration, and pneumothorax. Since the introduction of fissure analysis and Chartis measurement of collateral ventilation for patient selection, there has been a steady increase in the incidence of pneumothoraces, which has been estimated at 20% in the latest series [31]. Providing patients receive prompt treatment, those who experience a pneumothorax have a greater clinical response, and in these cases pneumothorax may even be considered as a predictor of success [32].

Nevertheless, a pneumothorax is a serious complication and therefore strict monitoring of patients within the first 72–96 h following intervention is crucial, as pneumothorax develops most often directly after treatment to within the first 4 days. An expert statement regarding the handling of pneumothorax has already been published [33].

The EBVs have now been used for more than 10 years, and 2 small long-term series have been published on these valves, the only removable endoscopic lung volume reduction technique at the moment. Both series showed a significant survival benefit in the successfully treated compared to the unsuccessfully treated group [34, 35].

Several trials using the EBVs are currently ongoing focusing on the optimal patient selection in patients with absence of collateral ventilation (LIBERATE trial, NCT01796392, and TRANSFORM trial, NCT02022683), long-term follow-up (LIVE study, NCT01580215), evaluation of outcomes of valve therapy in patients with more moderate COPD (REMODEL trial, NCT01969734) or in patients with a homogenous emphysema distribution (IMPACT trial, NCT02025205).

Although the IBV (Olympus) is commercially available, and has been investigated intensively, only one published small (n = 11) trial has shown efficacy [36]. The previously reported intended use of this device, i.e. in a nonlobar occluding bilateral approach, was not clinically effective, and has been abandoned [24, 36].

Coils

Lung volume reduction with coils (PneumRx/BTG, Camberley, UK) is a bronchoscopic bilateral implantation technique of several nitinol coils. The lung volume reduction is achieved by parenchymal compression due to the preformed coiled shape. Improved elastic recoil and changes in compliance as well as reduction of trapped airspace are possible mechanisms of actions [37].

First reports have demonstrated feasibility and safety of the procedure with encouraging results [38, 39]. The

RESET trial provided the randomized controlled evidence for this technology. Forty-seven patients were assigned 1:1 to the treatment or control group, and all treated patients received a bilateral coil implantation [40]. The trial showed statistically and clinically significant improvement in lung function [6MWT and St George's Respiratory Questionnaire (SGRQ): 8.11 vs. 0.25 points]. A multicenter European prospective single-arm trial on 60 patients confirmed the efficacy and demonstrated that the benefits were sustained for up to 1 year after treatment [41]. In a small series, it was suggested that coil implantation might also be an effective approach for patients with homogeneous emphysema [42].

The reported complications of the coil procedure are COPD exacerbations, hemoptysis, transient chest pain, pneumonia, and pneumothorax [37]. Most of the complications occurred in the first weeks following placement, and only mild hemoptysis was seen over time.

Two randomized controlled trials have recently been completed. A multicenter trial from France (n = 100) (NCT01822795) [43] has just reported its first results in abstract form showing in their intention-to-treat analysis the superiority of the LVRC group in the number of patients exceeding ≥54 m in the 6MWT at 6 months compared to the standard of care control group (36 vs. 17% of the patients, $p < 0.05$). A much larger RCT called the RENEW trial (NCT01608490), with 315 patients randomized 1:1 in over 30 centers in the US, Canada, and EU, has just been completed, with the first results expected in mid-2016. In this trial, the questions regarding preimplant selection criteria should be answered, in addition to evaluating the safety of the coil implant, as well as its effects on lung function, exercise capacity and quality of life.

Bronchoscopic Thermal Vapor Ablation

Bronchoscopic thermal vapor ablation (BTVA; Uptake Medical Corporation, Seattle, Wash., USA) consists of the instillation of heated water in the most destroyed lobe. Thereby, an inflammatory response is induced, which results in an irreversible parenchymal fibrosis and scarring and thus lung volume reduction.

The evidence level for BTVA is limited. In a subsequent multicenter single-arm trial, 44 patients with upper lobe predominant emphysema were studied [44]. The trial was able to show significant changes in FEV_1, vital capacity, 6MWT and SGRQ. A 12-month follow-up confirmed the sustainability of lobar volume changes [45]. However, despite the promising results in these first trials, a high number of serious adverse events occurred, possibly due to a cumulative high-energy dose used, and the approach had to be abandoned. The most common complication of BTVA was due to the induced inflammation. Most patients developed a severe local inflammatory reaction, associated with fever, cough, sputum, dyspnea, and hemoptysis. Most of the inflammatory reactions gradually resolve within 8–12 weeks after the procedure. Nevertheless, the inflammatory response can lead to a prolonged hospital stay. However, the local inflammatory reaction seems to be essential for the desired lobar volume reduction. Patients who developed respiratory adverse events following BTVA experienced a better clinical outcome [46].

Recently, the initial results of a randomized controlled multicenter trial (STEP-UP trial, NCT01719263) were presented in abstract form [47]. In this trial, much lower BTVA energy doses have been used, still showing significant results for FEV_1 and SGRQ, but with a safer event profile when compared to the previous BTVA efforts. Future trials, with longer-term follow-up, will have to confirm these early findings.

Biological Lung Volume Reduction

Biological lung volume reduction using the lung sealant system (AeriSeal) is another irreversible endoscopic lung volume reduction technique that employs a synthetic polymer to block small airways and collateral channels, promoting atelectasis, remodeling, and scar formation. This results in a reduction of hyperinflation. The technique is independent of collateral ventilation [48]. In open-label pilot studies, the sealant system durably reduced lung volume and improved lung function as well as quality of life, which was more pronounced in heterogeneous emphysema when compared to homogeneous emphysema patients [49, 50]. The most common side effects are comparable to the vapor technology.

Based on these feasibility results, an open-label, prospective, multicenter RCT in patients with advanced, upper lobe predominant emphysema was started (ASPIRE trial, NCT01449292). The study was terminated prematurely for business-related reasons after 95 out of 300 planned patients had been randomized. In the treatment group, the 3-month lung function, dyspnea, and quality of life improved significantly from baseline when compared to controls. Improvements persisted at 6 months with >50% of treated patients experiencing clinically important improvements; 44% of treated patients experienced adverse events requiring hospitalization with 2 deaths in the treated cohort. Treatment responders tended to be those experiencing respiratory adverse events [51]. This technology is currently undergoing further evaluation prior to further clinical trials.

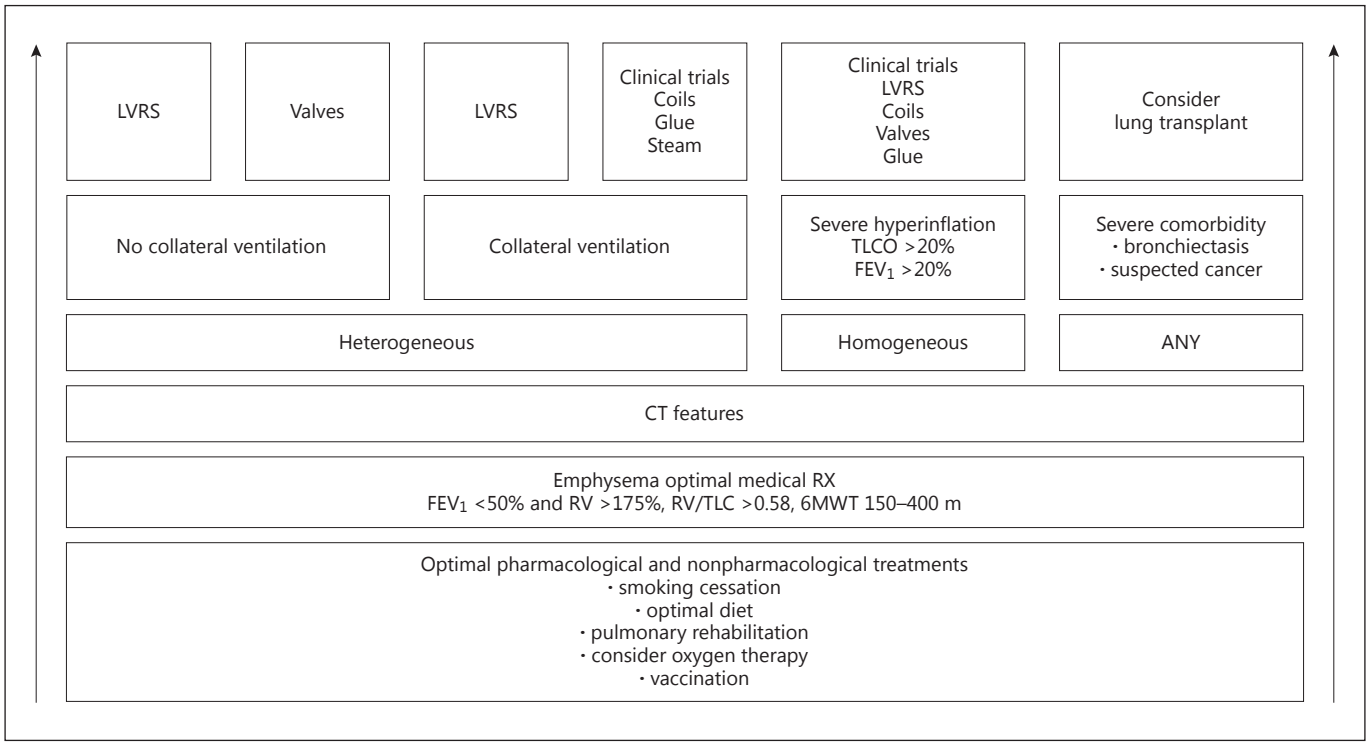

Fig. 1. Algorithm for the advanced treatment of severe emphysema patients.

Expert Algorithm

In a round table discussion starting at the end of 2014, an expert endoscopic panel developed the presented algorithm for the advanced treatment of severe emphysema patients, based on the above-presented literature (fig. 1). All emphysema patients considered should be on optimal pharmacological and nonpharmacological treatment in agreement with the actual GOLD recommendations or the national guidelines [1]. According to the panel members, active smoking is a clear contraindication.

Patients fulfilling these criteria should have a significant hyperinflation measured in the lung by body plethysmography. In the performed CT scan, other relative findings must be reported and might be the reason to stop further evaluation.

All qualified patients should be discussed by a multidisciplinary team including radiologists, pulmonologists, thoracic surgeons as well as an interventional pulmonologist.

For all patients, lung transplantation might be an option, and connection or easy access to a program is recommended. Therefore, this possibility should be considered as well. The transplant option is not a contraindication for endoscopic lung volume reduction [52]. It can therefore be elegantly used also as a bridging method.

Depending on the heterogeneity of the emphysema and the collateral flow, analyzed by the completeness of the fissure and confirmed with the Chartis system, the algorithm shown in figure 1 recommends the further options. Only LVRS and the EBV reached the evidence level to be used outside of clinical trials. However, both are recommended to still be used in registries.

Current endoscopic developments are significantly progressing as mentioned above, and will for sure add more input to the current algorithm. LVRS is still a valid treatment option; however, nowadays new surgical techniques are available and even more often used than the ones evaluated in NETT, thereby questioning the current validity of the NETT results. The new techniques look solid and promising in creative hands, but the science behind these developments is currently lacking. The evidence for endobronchial therapies is accumulating and the latter represent a viable alternative in selected patients.

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