Guidelines

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Endoscopic Lung Volume Reduction: An Expert Panel Recommendation – Update 2017

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Abstract
Interest in endoscopic lung volume reduction (ELVR) technologies for emphysema is consistently growing. In the last couple of months, several endoscopic options (e.g., endo- or intrabronchial valves, coil implants, and thermal vapor ablation) that have been evaluated in randomized controlled trials have been reported with the ultimate goal of improving respiratory mechanics and alleviating chronic dyspnea. Patients presenting with severe air trapping and thoracic hyperinflation have the greatest potential to derive benefit from ELVR procedures. Baseline assessment should ideally include cardiological evaluation, high-resolution computed tomography scan and perfusion scintigraphy, full pulmonary function tests, and cardiopulmonary exercise testing. This expert statement updates best practice recommendations regarding patient selection and utilization of these various techniques for the treatment of patients with advanced emphysema.

Introduction

Emphysema is a progressive and debilitating disease characterized by irreversible destruction of alveolar tissue. Emphysema is hallmarked by a reduction in lung elastic recoil, progressive hyperinflation, and air trapping. Patients experience chronic dyspnea, have limited exercise tolerance, and poor health-related quality of life. The most common cause of emphysema is cigarette smoking, although genetic, occupational, and environmental causes contribute to 10% of cases [1, 2]. Chronic obstructive pulmonary disease (COPD) is the fourth most common worldwide cause of death according to the WHO and will become the third worldwide cause of death by 2030 [3]. Patients with severe emphysema remain significantly disabled despite current best practices of medical care, pulmonary rehabilitation, and long-term oxygen supplementation. Medical treatment is unable to reverse or significantly reduce hyperinflation caused by alveolar destruction and, therefore, provides limited benefit.

Since 2002, several endoscopic interventions have been evaluated in clinical trials to reduce hyperinflation and thus improve breathing mechanics [4]. Endoscopic

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lung volume reduction (ELVR) bronchoscopic techniques could be subgrouped into reversible blocking techniques and irreversible nonblocking techniques. The choice of the different ELVR techniques depended on the distribution of emphysema and degree of collateral ventilation.

ELVR presents an encouraging therapeutic modality for patients with advanced emphysema. However, efficacy depends strictly on patient selection requiring an appropriate diagnostic and treatment algorithm for identifying the best candidates for each of the various ELVR techniques [5]. Complete lobar occlusion by valve implantation provides an effective option for patients with severe heterogeneous upper lobe or lower lobe predominant emphysema and nowadays for homogeneous patients as well. Hence, patient selection focuses on the integrity of the lobar fissures and the absence of collateral ventilation [6]. Irreversible nonblocking techniques are useful minimally invasive endoscopic approaches for patients with collateral ventilation. Therefore, accurate patient selection has great importance.

In 2016, an expert panel [7] published for the first time a possible treatment algorithm based on peer-reviewed evidence. Since then, several randomized controlled trials have been published which alter the treatment decisions previously outlined in the original 2016 Expert Panel Report. Based on the increasing level of evidence, the use of bronchoscopic lung volume reduction techniques has been adopted and incorporated into the 2017 update of the GOLD Report [8].

Patient Selection

The recommendation for the selection of patients for further evaluation remains unchanged [7]. Potential patients who are candidates for intervention are those who remain highly symptomatic despite receiving optimal medical treatment, i.e., maximal pharmacological therapy with bronchodilators, inhaled corticosteroids in selected candidates and sometimes maintenance of 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, complete lung function measurements, computed tomography (CT) scan of the thorax, and a 6-min walk test. Based on the available data, patients with severe and very severe airflow obstruction (i.e., GOLD stages 3 and 4, FEV_1 20–45%), who are highly symptomatic (grades C and D; Cognitive Ability Test scores ≥10, mMRC [modified British Medical Research Council] scores ≥2; hyperinflation, i.e., residual volume [RV] ≥175% or RV/total lung capacity ≥0.58); a reduced 6-min walk distance [6-MWD] of 100–500 m), may be considered for lung volume reduction therapies (Table 1). Severe pulmonary hypertension should be excluded. When an elevated right ventricular systolic pressure measured by echocardiography (>50 mm Hg) is identified, a right heart catheterization should be undertaken. In selected cases with pulmonary hypertension, endobronchial valve (EBV) placement may be considered following multidisciplinary discussion [9]. In our opinion, if they are excluded from valve placement due to pulmonary hypertension, they should not be considered suitable for any other current interventional or surgical procedures. Additionally, limited evidence has been published for successful valve treatment in emphysema patients with an FEV_1 <20% predicted [10, 11].

Radiological Assessment

Recommendations for the radiological assessment are more or less unchanged. Standardized noncontrast volumetric CT scans are required both to characterize the emphysema, degree of destruction on a lobar basis, evaluate the distribution of the emphysema destruction, and to determine the integrity of the lobar 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 [12]. If there are unexpected findings like bronchiectasis, pulmonary nodules, suspected lung cancer, interstitial fibrosis or severe tracheobronchomalacia that are identified on the high-resolution CT (HRCT) scan, patients should be evaluated and treated based on the abnormality if clinically important [7].

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 being less than –910 or –950 Hounsfield Units (HU) [13]. The –910 HU density threshold is commonly used for thick-slice (>3 mm) CT scans. This threshold yields the best correlation between emphysema as determined from resected lung tissue and 10-mm thick-slice CT measurements [14]. With the advent of multislice scanners, also using volumetric

Table 1. Baseline characteristics of the recently published RCTs

	STELVIO	IMPACT	REACH	RENEW	REVELONS	STEP-UP	TRANSFORM
Age, years	59	63.7	63.7	64	62	63,6	64
FEV_1, % predicted	30	29.4	27.2	26.0	26.3	33.4	30.8
RV, % predicted	217	275	261	245	270	238	245
6-MWD, m	367	308	335	307	313	362	291
Emphysema location	UL/LL	UL/LL	UL/LL	UL/LL	UL/LL	UL	UL/LL
Emphysema distribution	Homo/hetero	Homo	Hetero	Homo/hetero	Homo/hetero	Hetero	Hetero

UL, upper lobe; LL, lower lobe.

reconstructions, the density thresholds for emphysema for different scan settings have been reinvestigated [15]. 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 [16]. Several density thresholds have since been proposed for emphysema quantification, but for thin-slice volumetric chest CT scans, –950 HU is currently 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 CT processing software. Heterogeneity is the relative or percent 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 less than –910 HU or a >15% difference in the proportion of pixels of less than –950 HU has been used.

A complete fissure, also referred to as fissure integrity, as determined via qualitative assessment of CT scans, is thought to correspond to lack of interlobar collateral ventilation. HRCT fissure analysis has been performed for several years; however, only a few trials focus on patients with emphysema. These studies demonstrate the difficulty of the fissure analysis that presupposes a high degree of experience. One of the major limitations of evaluating fissures on CT scans by the human eyes is its subjective nature and inconsistency in quantifying the degree of integrity. Semi-automated software which evaluates the integrity of the fissure on a thin-slice CT scan has been developed by several companies. Based on the current knowledge, a patient with a fissure completeness of more than 85% on thin-slice HRCT on all three axis (sagittal, axial and coronal view) might be considered eligible for valve treatment [17]. Once again, this is possible visually with large interobserver variability, but more sophisticated software analysis produces more consistent results [18–20].

In a retrospective analysis, Schuhmann et al. [21] aimed to determine quantitative CT (QCT) predictors of ELVR outcome and compare the QCT model with Chartis in selecting likely responders to valve-based lung volume reduction treatment. Baseline CT scans of 146 subjects with severe emphysema who underwent EBV lung volume reduction were analyzed retrospectively using dedicated lung quantitative imaging software (Apollo; VIDA Diagnostics, Coralville, IA, USA). A lobar volume reduction greater than 350 mL at 3 months was considered to be indicative of positive response to treatment. Thirty-four CT baseline variables, including quantitative measurements of fissure integrity, density, and vessel volumetry, were used to feed a multiple logistic regression analysis to find significant predictors of ELVR outcome. The primary predictors were then used in 33 datasets with Chartis results to evaluate the relative performance of QCT versus Chartis.

Fissure integrity ($p < 0.0001$) and low attenuation clusters ($p = 0.01$) measured in the treated lobe and vascular volumetric percentage of patient's detected smallest vessels ($p = 0.02$) were identified as the primary QCT predictors of ELVR outcome. Accuracy for QCT patient selection based on these primary predictors was comparable to Chartis (78.8 vs. 75.8%). The authors concluded that QCT led to comparable results to Chartis for classifying collateral ventilation and is a promising tool to effectively select patients for valve-based ELVR procedures.

Based on the opinion of the expert panel, QCT analysis should be used if available.

The Technologies

Update on Endobronchial Valves

Since last year, several papers have been published. One of the major publications was: "Endobronchial valve therapy in patients with homogeneous emphysema. Results from the The IMPACT study" [22]. EBVs (Pulmonx) have been successfully used in patients with severe heterogeneous emphysema and complete fissures to improve lung physiology, but only limited available data suggest that EBVs are also effective in homogeneous emphysema. The IMPACT trial evaluated the efficacy and safety of EBVs in patients with homogeneous emphysema in the absence of collateral ventilation (assessed with the Chartis system). In this prospective, multicenter, 1:1 randomized controlled trial, EBV plus standard of care (SoC) or SoC alone was compared. The primary outcome was the percent change in FEV_1 (liters) at 3 months relative to baseline in the EBV group versus the SoC group. Secondary outcomes included changes in FEV_1, St. George's Respiratory Questionnaire (SGRQ), 6-MWD, and target lobe volume reduction. Ninety-three patients were allocated to either the EBV group (n = 43) or the SoC group (n = 50). In the intention-to-treat population, improvement in FEV_1 from baseline was 13.7% in the EBV group and –3.2% in the SoC group (p = 0.0002). Other variables demonstrated statistically and clinically significant changes from baseline to 3 months (EBV vs. SoC: SGRQ –8.6 vs. 1.0 and 6-MWD, 22.6 vs. –17 m). Target lobe volume reduction at 3 months was –1,195 mL (p = 0.0001). Of the EBV subjects, 97.2% achieved volume reduction in the target lobe (p = 0.0001). Procedure-related pneumothoraces occurred in 11 subjects (25.6%). Five subjects required removal/replacement of one or more valves. One subject experienced two valve migration events requiring removal/replacement of valves.

Recently, at the ATS meeting in Washington, Slebos et al. [23] presented the 6 months' data of the IMPACT trial. At 6 months, 87.3% of the initially treated patients met or exceeded the minimal clinically important difference for at least one of the endpoints (FEV_1: +100 mL, RV: –310 mL, 6-MWD: +26 m, and SGRQ: –4 points).

In conclusion, the IMPACT trial demonstrates that EBV therapy in selected patients with homogeneous emphysema without collateral ventilation results in clinically meaningful benefits of improved lung function, exercise tolerance, and quality of life. Given the limited treatment options available for this particular patient population, most notably limitations beyond medical therapy, EBV therapy should be considered in these patients.

A randomized controlled trial conducted in China in patients with heterogeneous emphysema was presented at the 2016 ERS international meeting in London (REACH trial) [24]. The REACH assessed the safety and effectiveness of EBV treatment for severe emphysema patients with complete fissures with the intrabronchial valve system of spiration (Olympus, USA). The study objectives were target lobe volume reduction (TLVR) and significant improvement in FEV_1. The full publication is still pending in this trial, which recruited 101 subjects, i.e., 66 treated and 35 control subjects. Target lobe selection, based on visual HRCT, identified an upper lobe in 55% and a lower lobe in 45% of patients. The control group received optimal medical management. 67% of patients at 6 months showed evidence of significant TLVR. Mean TLVR in treatment patients was 779 mL at 6 months. Compared to the control group, the treatment group achieved a significant and clinically meaningful improvement in FEV_1 at the 1-, 3-, and 6-month visits (16.8, 14.2, and 20.7%, respectively) with a responder rate of approximately 60% at these time periods. Significant improvements were also observed for quality of life measures and 6-MWD. There were 24 serious adverse events in the treatment group consisting primarily of acute COPD exacerbations (n = 12) and pneumothorax (n = 5). One in the control group died, whereas none in the treatment group. Also, this randomized controlled trial reached its primary effectiveness endpoint and demonstrated sustained clinically meaningful benefit with acceptable adverse events for severe emphysema patients selected only by HRCT. The achieved effectiveness and safety is comparable to the other valve system; however, they have not been evaluated head to head.

An update of the STELVIO trial [25] has been published in the last few months. In the STELVIO trial, the best responder criteria to EBV treatment were evaluated in a randomized controlled trial, using the Chartis system as primary treatment assessment tool [26]. Eighty-four patients were recruited, having >90% complete fissures on CT, 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 in change of FEV_1: +140 mL (95% CI 55–225), FVC: 347 mL (95% CI 107–588) and 6-MWD +74 m (95% CI 47–100), with an overall clinical significant responder rate to the treatment of 75%.

Klooster et al. [26], in their actual publications, presented the 12-month data as well as the data of the control

patients who crossed over to receive EBV 6 months after completion of the control endpoint assessment [27]. Therefore, 64 patients received EBV treatment. At 1 year, 40 patients were evaluated. Significant improvements ($p < 0.001$) were found for FEV_1 (+17%), RV (–687 mL), 6-MWD (+61 m), and SGRQ (–11 points). Two patients died: 1 after 58 days due to progressive respiratory failure and 1 after 338 days of follow-up due to a myocardial infarction.

In 22% of the patients, pneumothoraces occurred before 6 months, and none occurred between 6 and 12 months. These data clearly demonstrate that EBV treatment in well-selected patients results in clinically relevant benefits at 1 year of follow-up. This study supports the use of EBV treatment in carefully selected patients with severe emphysema without collateral ventilation [27].

Recently, at the ATS meeting in Washington, the data of another multicenter, randomized trial (TRANSFORM) with the Zephr valve (Pulmonx Inc., Redwood, CA, USA) was presented [28]. Ninety-seven subjects (♂/♀: 58/39; mean age: 64.0 years) were randomized and the 3-month postprocedure data have been presented. The FEV_1 change was 32%, RV decreased by 14%, 6-MWD improved by 64 m and the SGRQ improved by 10 points in the treated group compared to SoC. Comparable to the previous trial, the main complication was again pneumothoraces in 25.5% of EBV treated versus 0% of control subjects, followed by COPD exacerbations in 4.3 versus 3.8% of subjects, respectively. The data from this trial confirmed the findings of the STELVIO study.

In all the above-mentioned trials, a postprocedural pneumothorax was the most common side effect. In cases where rapid TLVR occurs, an increase in pneumothorax risk is encountered due to parenchymal rupture of the adjacent nontreated lobe [29].

In a retrospective analysis, the impact of pneumothorax on outcome following EBV treatment was analyzed [30]. All patients had undergone chest X-ray within 24 h of EBV implantation to explore the presence of pneumothorax. TLVR and the clinical outcome measures FEV_1, SGRQ, and 6-MWD were assessed 180 days after implantation. The median time to the onset of pneumothorax after valve placement was 2 days. However, patients who experienced a pneumothorax benefitted from EBV therapy. The mean percent change in FEV_1 was 15 ± 15%, and the mean change in SGRQ was –7 ± 12 points. The conclusion of the analysis clearly showed that a pneumothorax is a complication of EBV placement, but it does not appear to have a negative impact on clinical outcome in terms of FEV_1 and health-related quality of life. As pneumothorax is an anticipated complication of EBV therapy, close monitoring for the development of a pneumothorax following the intervention is necessary.

For the handling of a pneumothorax, the panel still recommends the "Expert statement: pneumothorax associated with endoscopic valve therapy for emphysema – potential mechanisms, treatment algorithm, and case examples" published by Valipour et al. [31].

Coils

Two randomized controlled trials have recently been completed and published.

A multicenter French randomized controlled trial (n = 100 patients; REVOLENS trial) was published in early 2016 [32]. In this multicenter, 1:1 randomized trial, the efficacy, safety, cost, and cost-effectiveness of nitinol coils in the treatment of severe emphysema was compared with usual care at 10 university hospitals in France. All patients received rehabilitation and bronchodilators with or without inhaled corticosteroids and oxygen; those randomized to bilateral coil treatment (n = 50) received usual care plus additional therapy in which approximately 10 coils per lobe were placed in 2 bilateral lobes in 2 separate procedures. The primary outcome was an improvement of at least 54 m in the 6-MWD at 6 months. Secondary outcomes included changes at 6 and 12 months in the 6-MWD, lung function, quality of life (SGRQ), morbidity, mortality, total cost, and cost-effectiveness. One hundred patients were included. At 6 months, improvement of at least 54 m in the 6-MWD was observed in 18 patients (36%) of the coil group and in 9 patients (18%) of the usual care group. The mean between-group differences at 12 months in the coil and usual care groups were +0.08 L for FEV_1, +21 m for 6-MWD, and –10.6 points for SGRQ. Within 12 months, 4 deaths occurred in the coil group and 3 in the usual care group. The mean total 1-year per-patient cost difference between groups was USD 47,908 and the incremental cost-effectiveness ratio was USD 782,598 per additional quality-adjusted life-year.

Pneumonia was the most frequent serious adverse event (18%) in the coil group and there were 2 events in 2 patients (4%) in the usual care group within 1 year. Overall, at least 1 serious adverse event occurred within 1 year in 26 patients (52%) in the coil group and in 19 patients (38%) in the usual care group.

The authors concluded that bronchoscopic treatment with nitinol coils compared with usual care improved exercise capacity but was associated with high short-term costs. Further investigation is needed to assess the durability of benefit and long-term cost implications.

The largest trial of lung coil technology was presented at the ATS 2016 conference and simultaneously published in Sciurba et al. [33]. In this randomized clinical trial conducted among 315 patients with emphysema and severe air trapping recruited from 21 North American and 5 European sites, the effectiveness and safety of endobronchial coil treatment was examined. Patients were randomly assigned to continue usual care alone (guideline based, including pulmonary rehabilitation and bronchodilators; $n = 157$) versus usual care plus bilateral coil treatment ($n = 158$) involving 2 sequential procedures 4 months apart in which 10–14 coils were bronchoscopically placed in a single lobe of each lung. The primary effectiveness outcome was the difference in absolute change in 6-MWD between baseline and 12 months (minimal clinically important difference, 25 m). Secondary endpoints included the difference between groups in 6-MWD responder rate, absolute change in quality of life using the SGRQ and change in FEV_1. The primary safety analysis compared the proportion of participants experiencing at least 1 of 7 prespecified major complications. Among 315 participants, 90% completed the 12-month follow-up. Median change in 6-MWD at 12 months was 10.3 m with coil treatment versus −7.6 m with usual care, with a between-group difference of 14.6 m ($p = 0.02$). Improvement of at least 25 m occurred in 40.0% of patients in the coil group versus 26.9% with usual care. The between-group difference in median changes in FEV_1 was 7.0% and the between-group difference in SGRQ scores was –8.9 points ($p < 0.001$), favoring the coil group. Major complications (including pneumonia requiring hospitalization and other potentially life-threatening or fatal events) occurred in 34.8% of coil participants versus 19.1% of patients receiving usual care ($p = 0.002$). Other serious adverse events including pneumonia (20% coil vs. 4.5% usual care) and pneumothorax (9.7 vs. 0.6%, respectively) occurred more frequently in the coil group.

Therefore, the overall results of the RENEW trial showed among patients with emphysema and severe hyperinflation treated for 12 months that the use of endobronchial coils compared with usual care resulted in an improvement in median exercise tolerance that was modest and of uncertain clinical importance, with a higher likelihood of major complications. Further follow-up is therefore needed to assess the long-term effects on health outcomes.

In a prespecified analysis, participants were stratified into 4 subgroups based on characteristics associated with lung hyperinflation and emphysema.

Participants with both favorable attributes (RV ≥225% predicted and heterogeneous distribution) exhibited superior treatment responses (median 6-MWD +29.1 m, FEV_1 change +12.3%, and mean SGRQ, –10.1-point difference in the coil group relative to usual care), while those with less air trapping (RV <225% predicted) and homogeneous disease exhibited between-treatment differences of a median of –16.7 m for 6-MWD, a median FEV_1 change of 3.5%, and a mean SGRQ change of –3.3 points.

Actual various analyses of both datasets are calculated. The panel expected possible additional predictors as an outcome of those analyses. These predictors have to have their effectiveness demonstrated in future prospective randomized controlled trials. Therefore, at present, the recommendation is to use the endobronchial coils only in patients with an RV >225%. Those patients should be enrolled in a registry to gain further insights into the technologies. All other patients should only be treated in controlled trials.

Bronchoscopic Thermal Vapor Ablation

Bronchoscopic thermal vapor ablation (Uptake Medical Corporation, Seattle, WA, USA) creates volume reduction by the instillation of heated water in the most destroyed lobe. An inflammatory response is focally induced which provokes irreversible parenchymal fibrosis and scarring and thus targeted lung reduction in emphysematous tissue.

Recently, the 6-month as well as the 12-month results of a randomized controlled multicenter trial (STEP-UP trial) were reported [34, 35]. In this trial, the technique was used in a step-up approach. This is a particularly useful strategy whereby segments within a lobe are substantially more diseased than others, thereby warranting a more targeted approach of the more emphysematous subcomponents of a lobe. The STEP-UP study evaluated whether or not selective sequential treatment of the more diseased upper lobe segments with bronchoscopic vapor ablation led to clinical improvement. The primary efficacy endpoints were statistically significant changes in FEV_1 and SGRQ scores between the trial groups at 6 months, analyzed by an intention-to-treat analysis.

Seventy patients were enrolled and randomly assigned in a 2:1 approach. After 6 months, the mean relative improvement in FEV_1 was 14.7% ($p < 0.0001$) and in SGRQ –9.7 points ($p = 0.0021$). COPD exacerbation was the most common serious adverse event, occurring in 11

Table 2. Results of the trials

Study, year	Patients treated, *n*	Device	Follow-up duration, months	ΔFEV_1, mL	ΔRV, mL	Δ6MWD, m	ΔSGRQ, points
Klooster et al. [25] (STELVIO), 2017	40	EBV	12	147	−672	61	−11
Li et al. [24] (REACH), 2016	58	IBV	6	108	NA	42	−12.8
Valipour et al. [22] (IMPACT), 2016	43	EBV	3	120	−480	40	−9.6
Slebos et al. [23] (IMPACT), 2017	43	EBV	6	120	−430	28	−7.6
Deslee et al. [32] (REVELONS), 2016	50	coils	12	80	−360	36% improvement ≥54 m	−10.6
Sciurba et al. [33] (RENEW), 2016	158	coils	12	50	NA	15	−8.9
Herth et al. [34] (STEP-Up), 2016	44	steam	6	131	−303	31	−11.1
Shah et al. [35] (STEP-Up), 2016	44	steam	12	103	−240	4	−12.1
Kemp et al. [28] (TRANSFORM), 2017	65	EBV	6	230	−670	79	−6.5

IBV, intrabronchial valve.

(24%) of 45 patients in the treatment group and in 1 (4%) of 24 in the control group. No pneumothorax occurred within 30 days of treatment.

Compared to standard medical management, targeted thermal vapor ablation of the more diseased segments and preservation of the less diseased segments resulted in clinically meaningful and statistically significant improvements in lung function and quality of life at 6 months, with an acceptable safety profile.

Meanwhile, the 12-month data have been published. Shah et al. [35] was able to show a durable improvement over time. The between-group difference was 12.8% (p = 0.0039) for FEV_1 and −12.1 units (p = 0.0021) for SGRQ at 12 months. The secondary endpoint changes in RV showed an average reduction of 237 mL over the control group. During the 12-month follow-up, the majority (71%) of respiratory-related serious adverse events occurred in the first 90 days following treatment. All of these respiratory-related serious adverse events resolved with standard medical care with the exception of 1 patient death, secondary to a COPD exacerbation. In the period of 90–360 days following treatment, the rate of serious adverse events between the treatment arm and the control arm were equivalent; respiratory-related serious adverse events were experienced by 16% of treatment patients and by 17% of control patients in the period.

Therefore, compared with standard medical management, targeted thermal vapor ablation of more diseased segments and preservation of less diseased segments resulted in clinically meaningful and statistically significant improvements in lung function and quality of life at 6 and 12 months, with an acceptable safety profile.

The limitation of targeted thermal vapor ablation is the restriction to upper lobe, heterogeneous diseased patients. At this time, the panel recommends the therapy only for those patients, and to be only performed in clinical trials. Trials in homogeneous and lower lobe patients have already begun and the results are expected by late 2018.

Biological Lung Volume Reduction

Biological lung volume reduction, using the lung sealant system (AeriSeal) is another irreversible ELVR technique that employs a synthetic polymer to block small airways and collateral channels, promoting atelectasis, remodeling, and scar formation. Several initial trials showed efficacy, but also significant adverse events precipitating the initial product to be withdrawn from clinical use [36]. The doses of the agent as well as the instillation methods are currently being studied in early-phase studies. Therefore, this technology is currently undergoing further evaluation (NCT02877459) and can only be in clinical trials in well-selected centers (Table 2).

Expert Algorithm

An initial consensus meeting followed by further panel discussions led to the development of the original algorithm in 2014. Such has been the development in this field that the expert endoscopic panel felt an update was required. The updated algorithm for the advanced treatment of severe emphysema patients, based on the abovementioned literature is presented in Table 3. All emphysema patients considered should be on optimal pharmacological and nonpharmacological treatment accord-

Table 3. Recommended algorithm

<table>
<tr><td>LVRS</td><td>Valves</td><td>Valves</td><td>Coils (RV >225%)
trial steam/coils
(RV 175–225%)</td><td>Coils (RV >225%)
LVRS steam
(registry)</td><td>Trial steam (LL)/
foam/coils
(RV 175–225%)</td><td>Coils
(RV >225%)</td><td>Trial steam/foam/
LVRS/coils
(RV 175–225%)</td><td rowspan="4">Consider
lung
transplant</td></tr>
<tr><td colspan="2">Heterogeneous</td><td colspan="2">Homogeneous</td><td colspan="3">Heterogeneous</td><td colspan="2">Homogenous</td></tr>
<tr><td colspan="4">FI complete/Chartis negative</td><td colspan="4">FI incomplete/Chartis positive</td></tr>
<tr><td colspan="8">Fissure integrity/Chartis</td></tr>
<tr><td colspan="9">Emphysema optimal medical treatment
FEV_1 <50% and RV >175%, RV/TLC >0.58, 6-MWD 150–44 m</td></tr>
<tr><td colspan="9">Optimal pharmacological and nonpharmacological treatments
– Smoking cessation, optimal diet, vaccination
– Pulmonary rehabilitation
– Consider oxygen therapy</td></tr>
</table>

LVRS, lung volume reduction surgery; FI, fissure integrity; TLC, total lung capacity.

ing to the latest GOLD recommendations or the national guidelines. Active smoking is a clear contraindication to these advanced endoscopic therapies in the opinion of the panel members. Following the recommendation from 2016 patients fulfilling these criteria should have significant hyperinflation measured in the lung function by body plethysmography. In the performed CT scan, other relative findings must be reported and coexistent disease that may preclude treatment excluded. All suitable patients should be presented to a multidisciplinary team discussion 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. The option of transplantation is not a contraindication for ELVR [37] and the techniques can be used as a bridging strategy.

Only lung volume reduction surgery and EBVs reached the evidence level to be used outside of clinical trials. However, both are recommended to still be used in registries.

Furthermore, there are active randomized trials for every technology ongoing. Future discussions of the algorithm are planned to give a clear and evidence-based recommendation to the community.

Broader treatment has demonstrated new challenges and unusual complications and hence clinical experience should be concentrated in the early phase of introduction of these therapies. Therefore, the panel also advises that patients should be treated in expert/high-volume centers, which are participating in clinical trials and registries to capture all treatments, when performed outside clinical trials.

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