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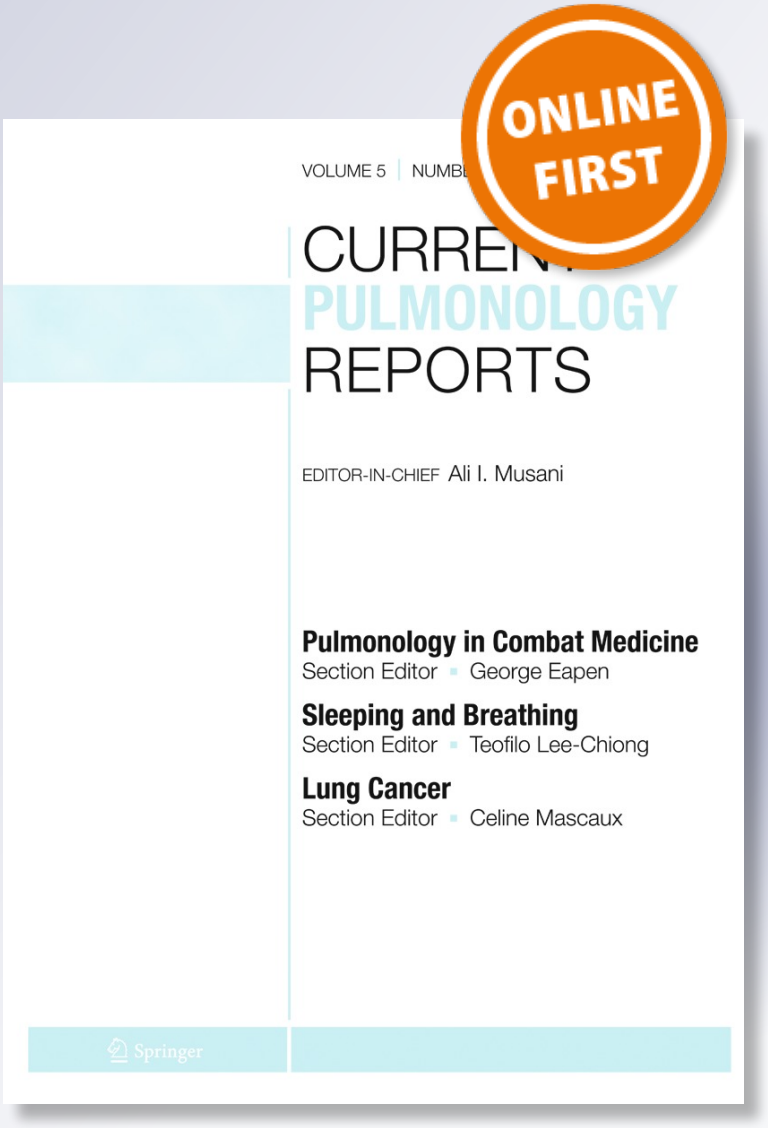

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INTERVENTIONAL PULMONOLOGY (L SEIJO, SECTION EDITOR)

The importance of patient selection for lung volume reduction

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Abstract COPD is one of the main causes of morbidity and mortality worldwide. It is a progressive disease for which there is currently no cure, limiting activities of daily living and worsening patients' quality of life. Emphysema involves the destruction of the lung parenchyma, the main pathogenic manifestation of which is pulmonary hyperinflation, which limits airflow and exercise impairment. In recent years, several treatments have been developed to reduce lung volume and improve ventilatory mechanics. Surgical treatment was used initially, though the high rate of mortality and perioperative complications has caused this treatment be reserved for a select subset of patients. More recently, various endoscopic devices have appeared. There are several ongoing studies aimed at assessing the efficacy and safety of these procedures. Not all patients diagnosed with emphysema are candidates for this treatment and accurate patient selection is essential for achieving positive outcomes.

Keywords COPD · Endoscopic lung volume reduction · Emphysema · Hyperinflation · Endobronchial valves · Coils

Introduction

Chronic obstructive pulmonary disease (COPD) comprises a number of pathological entities which result in irreversible airway obstruction. COPD is the third leading cause of death worldwide [1] and one of the main causes of loss of quality of life, premature death, and years lived with disability [2]. The prevalence of this pathology is estimated to be around a 7.6 % though showing substantial regional variability [3]. In Spain, it is estimated that there are about two million patients between the ages of 40 and 80 years with COPD symptoms, most of whom are men [4].

COPD therapy may include both pharmacological (mainly bronchodilators) and non-pharmacological measures (respiratory rehabilitation). These treatments do not cure the disease and aim to control the symptoms and diminish the risk of exacerbations derived from progressive worsening of lung function [5].

COPD with the presence of emphysema is characterized by the progressive and irreversible destruction of alveolar spaces, causing a loss of available surface for gas exchanging, as well as premature airway collapse [6]. As a result, air becomes trapped in the lungs, during expiration, thus causing hyperinflation, the main pathological feature of the disease. This condition is aggravated by the increase in respiratory rate (dynamic hyperinflation), which in daily life is triggered during exercise and can be evaluated with laboratory stress tests or by increasing the number of respirations per minute in a controlled manner [7, 8]. Otherwise, the loss of the normal lung structure leads to an alteration in pulmonary dynamic owing to diminished pulmonary recoil and increased lung volumes beyond resting values. This situation causes an overload for the respiratory musculature and a restriction of tidal volume during exercise [9].

Regarding this pathogenic phenomenon, several novel therapeutic approaches have been developed to complement the standard treatment by reducing the amount of trapped gas in the lung. In 1957, Brantigan and Mueller carried out the first surgical treatment of emphysema [10]. The NETT (National Emphysema Treatment Trial) study, a multi-center,

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prospective, randomized, controlled trial comparing treatment, evaluated the risks and benefits of surgical lung volume reduction in 1218 patients [11, 12]. The study found that in order to achieve clinically relevant results, patient selection had to be rigorous due to high perioperative morbidity and mortality.

Based on findings of this study, endoscopic lung volume reduction techniques now offer new possibilities for treatment of advanced emphysema, decreasing the risk of complications associated with the surgery.

Techniques available

Since the advent of endoscopic lung volume reduction, several devices and systems have been proposed. Some like the Watanabe "Spigots" (Novatech, La Ciotat, France) have been displaced due to the scant evidence on their effectiveness. Alternatives have been created, such as the "Airway By pass" Stent (Broncus Technologies, San Jose, CA, USA), based on joining emphysematous zones to the airway in order to allow the evacuation of the trapped air, although this system has only been proven to be effective over the short-term.

A number of polymeric substances have also been developed, such as the Aeriseal® (Aeris Therapeutics, Woburn, MA, USA) which works as a glue in the lung areas where the polymer was inserted, achieving atelectasis and fibrosis. Using this system, one multi-center clinical trial was carried out, achieving promising results [13]. For the moment, however, it has fallen into disuse due to commercial issues.

A randomized, multicentric study (STEP-UP trial) was published by Herth et al. [14] in which a segmentary treatment was performed in patients with upper lobe-predominant heterogeneous emphysema using thermal vapor ablation. The high temperature produced by the technique presumably causes an inflammatory reaction which favors the appearance of atelectasis and scar fibrosis. After 6 months, an improvement was seen in FEV1 and in Saint George Respiratory Questionnaire (SGRQ). Despite these results, this treatment is not one of the most widely implemented treatments available for lung volume reduction.

Nowadays, the most commonly used devices and those for which there is most evidence are unidirectional valves and coils.

Unidirectional valves

There are two models used for this purpose. The most widely used is the ZEPHYR® valve system (EBV; Pulmonx Inc. Redwood City, CA, USA) although intrabronchial valves (IBV Olympus Respiratory America, Redmond, WA, USA) are also available. Both are self-expanding devices, placed using a catheter inserted through the bronchoscope working channel (2.8 mm in diameter). Valves treatment is reversible and can be removed in case of dysfunction, lack of clinical improvement, or recurrent infections.

There has been broader experience with the ZEPHYR model; the VENT study, published in 2007, was the first prospective, randomized, multi-center study to assess this treatment [15] comparing it with standard treatment without valve placement. The inclusion criteria were derived from the NETT study. One of the objectives of this trial was to characterize the profile of patients who would benefit from this treatment.

In the subgroup analysis of the VENT study, it was observed that patients in whom complete lung fissures were observed using CT scan, showed better treatment response. To prove this hypothesis, several studies have been published such as the BeLieVer HIFi study [16] where 50 patients with heterogeneous emphysema and complete lung fissure observed using CT scan were randomized to conventional treatment with or without valves (masking with a sham bronchoscopy). The treatment group showed a significant improvement in FEV1 at 3-month follow-up.

With the same purpose, Klooster et al. [17•, 18] published the STELVIO study, where 68 patients without evidence of collateral lobar ventilation, assessed using the Chartis® system (Pulmonx, Redwood City, CA, USA), were randomized to treatment or treatment plus EBV. This study showed a significant improvement at 6 months in FVC, FEV1, and 6-min walking test (6MWT).

Regarding treatment with endobronchial valves (EBV), several studies have explored relevant about technical issues and implant location.

In a trial published by Eberhardt et al. based on a subgroup population included in the VENT study with complete lung fissure or lobar exclusion, the authors analyzed whether there were differences between upper lobe treatment (45 patients with predominant upper lobe emphysema) and lower lobe treatment (15 patients with predominant lower lobe emphysema) finding no differences between the two [19].

The Heidelberg group also analyzed whether any difference existed between unilateral complete lobar occlusion and bilateral partial treatment with IBV, obtaining better improvement in functional parameters and quality of life in the first group [20].

More recently, Eberhardt et al. [21] published a series of six patients with pulmonary hypertension assessed by right heart catheterization treated with EBV. Five of them achieved an improvement in functional and hemodynamic parameters. Although it is the first case series of its kind, it may be a starting point for larger studies and represent a therapeutic alternative for this group of patients.

Though it is not part of routine clinical practice, in selected cases with bilateral lobar exclusion, bilateral treatment with EBV with years between both procedures seems to improve clinical and functional outcomes [22]. We strongly recommend unilateral valve treatment; however, in cases without

symptomatic improvement in which atelectasis is not accomplished, we encourage treatment of the contralateral lung after 6 months of follow-up and under protocol-guided clinical assessment.

Lastly, a multi-center, double-blinded, randomized, and controlled (standard-care group) study was carried out using IBV valves. In the treatment group, bilateral partial lobar occlusion was performed, with no significant differences between the groups [23].

COILS

COILS (RePneu®, BTG Inc, Mountain View, CA, USA) are spiral-shaped devices made of nitinol. Although more sizes are available, the most common have a length of 100,125, or 150 mm. Coils treatment is performed bilaterally in two procedures with a 4- to 6-week waiting period between them, except in the event of complications. The interventions are usually performed under general anesthesia though conscious sedation is feasible in some cases. Placement is performed under radioscopic control and using a positioning system provided by the manufacturer which permits insertion by means of a semi-rigid catheter through the bronchoscope working channel (2.8 mm) [24]. Location selection and choice of size are decided by using a guide which permits the semi-rigid catheter safely advance along the channel, reducing the risk of complications.

Although it can be removed during the first month, this treatment is initially considered irreversible. Indication is independent of collateral lobar ventilation and emphysema characteristics [25, 26].

In 2014, Deslee et al. [27] conducted the first European multi-center study of coils treatment aiming to evaluate the treatment's efficacy and safety. Sixty patients were recruited (55 with bilateral and 5 with unilateral treatment), and an average of 10 coils were used per lobe. A significant improvement in SGRQ, 6MWT, and RV was observed at 6-month follow-up, with the improvement remaining stable throughout the first year. Despite certain complications such as COPD exacerbation or pneumonia, a good security profile was found.

Similarly, the publication by Zoumot et al. [28] using a crossover design to study 45 patients treated bilaterally with coils, found an improvement in SGRQ, FEV1, and 6MWT at 180 and 360 days of follow-up reporting a good safety profile.

Based on this and other trials, the meta-analysis published by Slebos in 2015 [29] which included a total of 140 patients, found improvement in quality of life and respiratory function parameters confirmed after 1 year. No differences were found between treatment of heterogeneous and homogeneous emphysema patients, and a better response was observed in cases with higher RV.

The longest follow-up period in a study of coil-treated patients published to date is that of Hartman [30]. Over a 3-year assessment period in a group of 22 patients, it noted the initial 6MWT and SGRQ improvement in a remarkable percentage of the patients. Moreover, no complications related to coils (pneumothorax, infections, device migration, etc.) or deaths due to treatment occurred.

The most recently published multicenter, randomized, controlled study of to coil treatment is the REVOLENS study [31•]. The main objective was to assess efficacy, safety, and cost-effectiveness in 50 patients randomized to bilateral treatment with coils or control group, at 6- and 12-month follow-up. The efficacy parameters were >54 m of 6MWT, other functional results, and SGRQ. The authors found a significant improvement in the treatment group, though with high short-term costs.

Patient selection for endoscopic lung volume reduction

Patients considered to be eligible for this treatment are those symptomatic patients diagnosed with severe emphysema with remarkable hyperinflation without frequent exacerbations and no important comorbidities.

Except for slight variations depending on the center or investigator, the inclusion and exclusion criteria are those shown in Table 1.

When a patient is referred for lung volume reduction assessment, the first step is to perform a complete review of their medical history, including important factors such as smoking, previous respiratory diseases, cardiovascular comorbidities, standard treatment, and functional status. Quality of life questionnaires are completed during the first visit (mainly SGRQ and mMRC).

Regarding the mMRC scale, it is considered that a patient is a good candidate when they have a value over 2 points, though in several clinical trials and in common practice, it is feasible to treat patients with mMRC = 2.

The patient is usually referred by another respiratory specialist and may have high expectations about the potential results of the treatment. It is essential that the patient be clearly informed about the real goals of the treatment and the eventual complications related to the procedure. It is also important to show the patient the different devices available and their characteristics, making clear that the interventionism team will select the most optimum treatment for their case.

There is a wide range of diagnostic tests that should be performed for assessment and treatment selection.

Pulmonary function tests

Pulmonary function tests (PFTs) are a mainstay in patient evaluation and several of the inclusion criteria come from these tests.

Table 1 General inclusion and exclusion criteria for ELVR with endobronchial valves and COILS

Inclusion criteria
COPD emphysema phenotype
Non-current smoker
Optimal treatment including rehabilitation program
FEV1 20–50 %
RV > 175–200 (depending on the device)
TLC > 100 %
DLCO > 20 %, <50 %
6MWT > 150 m
mMRC > 1
Exclusion criteria
Positive bronchodilator test: >15 % variation in FEV1
More than 3 exacerbations per year
Chronic hypercapnia with BiPAP assistance needed
Significant comorbidities affecting survival
For coil treatment
Pulmonary hypertension with PAP > 50 mmHg assessed by echocardiography
Giant bullae more than 1/3 of the total lung volume or more than 8 cm of diameter
Severe emphysema with important lack of parenchyma
Chronic anticoagulant or antiplatelet treatment

This chart has not been yet published and was created by the authors

a. Spirometry

It is necessary to perform a basal maneuver and bronchodilator test, as a variation of over 20 % in FEV1 or a 200-cm^3 gain may lead to treatment rejection. An ideal value is considered to be below 45 % and over 20 % of FEV1.

b. Carbon monoxide diffusing capacity (DLCO)

It is considered that a DLCO value below 20 % is a contraindication for the treatment as this has been demonstrated to be predictor of high perioperative mortality [32, 33]. On the other hand, the recently published REVOLENS study [31•] has included patients with diffusion values below 20 %.

c. Plethysmography

This pulmonary-function test provides the most information for patient assessment. Regarding residual volume (RV) values, the first studies of lung volume reduction such as NETT [11] or VENT [15] placed the cut-off point at 150 %. This value, on the one hand, seems to be a good reference for endobronchial valve treatment [33]. However, it has been proposed that RV > 175–200 is related to better outcomes in coil treatment [29, 34••] and even randomized trials have chosen an RV cut-off point higher than 220 % [31•].

Regarding other values obtained using plethysmography, total lung capacity (TLC) should be over 100 % to consider the patient as a candidate for lung volume reduction. For this, VR/TLC ratio has to be over 58 % [34••].

There are other, less common tests of pulmonary function, like optoelectonric plethysmography which makes it possible to study changes secondary to hyperinflation such as asynchronic chest-wall movements. Zoumot et al. assessed the influence of lung volume reduction in these changes, noticing harmonization of chest-wall movement in treated patients and proposing the addition of this test within patient selection [35].

d. Six-minute walk test (6MWT)

This test evaluates the functional situation of the patient, measuring the distance covered during a set period of time. It has the advantage of being reproducible, although it may vary substantially due to the training effect or differences in patient motivation.

Based on documents published by ERS and ATS, it is estimated that the minimum significant difference is between 25 and 33 m [36]. Despite this fact, some studies, such as REVOLENS, have argued in favor of using longer distance (54 m) that determines response to the treatment based on a trial previously published [37].

It is estimated that, to be selected, the patient must walk between 100 and 500 m in the 6MWT after having completed a rehabilitation program.

Imaging tests

a. Chest computed tomography (CT scan)

This is one of the key tests for the selection and follow-up of patients undergoing lung volume reduction.

The main objective is to rule out comorbidities which contraindicate the treatment such as bronchiectasis, giant bullae (more than one third of the lung volume) or suspicious pulmonary nodules.

Moreover, involvement of a radiologist makes it possible to determine the characteristics of emphysema and this information will guide the type of treatment and the target location [38]. The quantification threshold that has shown a better correlation for emphysema assessment is −950 Hounsfield units (HU) in 1-mm slides in a non-contrast CT scan. To define emphysema as hetero- or homogeneous, a difference greater than 15 % in "the emphysema score" between two ipsilateral lobes is needed [34••].

In most cases, this emphysema characterization is a determining factor when choosing among the available treatments. In homogeneous emphysema, the greatest efficacy is seen with coils, while in heterogeneous emphysema, a more common finding, further studies are required to make the decision.

Another important source of input for CT scan is the assessment of lung fissures. Complete visualization of these structures is associated with the absence of collateral ventilation and suggests a better response to valve treatment. Several studies have sought to correlate radiologic findings, and it is proposed that a fissure is complete when 85–90 % is seen in either axis [33, 34••].

Several systems are used for emphysema quantification through CT imaging. The most widely used, even in the context of clinical trials, are software programs which quantify emphysema degree, emphysema distribution per lobe, and fissure integrity; examples of these include VIDA (VIDA Diagnostics Inc., Cupertino, USA), Myrian (Intrasens, Paris, France), and MeVisPULMO 3D (Fraunhofer MEVIS, Bremen, Germany) [39].

In a study of 33 patients published by Alves et al. [40], it was observed that dynamic hyperinflation can influence measurements and simulate emphysema progression. To avoid this, the authors propose inclusion of a rest period prior to the test

The role of CT in emphysema quantification goes beyond patient selection and emphysema characterization appears to be an indicator of treatment response as indicated by Fiorelli [41] in his study of 25 patients programmed to receive valve treatment for lung volume reduction.

b. Ventilation and perfusion scintigraphy

This test is not considered strictly necessary in the routine evaluation protocol for patient selection. Even though it does not provide information on hyperinflation, it can be an accurate indicator or pulmonary damage.

Concerning this test, a recently published study assessed the ventilatory and circulatory changes occurring after lung volume reduction with valves. Twenty-six patients exhibited substantial reduction of perfusion in the treated lobe, with an increase of perfusion and ventilation in the contralateral lung as an adaptive mechanism after the procedure [42].

Assessment of interlobar collateral ventilation

Evaluation of collateral ventilation is key to the assessment and selection of patients for lung volume reduction. As previously mentioned, CT scan can be a useful tool for this purpose, since complete visualization is strongly correlated with the absence of collateral ventilation and is a good predictor of response to endobronchial valve treatment [43, 44].

The other device available for this objective is the Chartis system (Pulmonx Corp., Redwood City, CA, USA). This device consists of introducing a balloon catheter through the bronchoscope working channel, occluding the target bronchi in the inspiratory phase and allowing expiratory flow through the catheter [17•]. The presence of continuous expiratory flow after 2 or more minutes of assessment is indicative of collateral ventilation presence. Otherwise, fall in expiratory flow, with increased airway resistance and pressure, suggests absence of collateral ventilation.

This test has become standard practice for patient selection, though in some centers, its high cost may restrict application.

In a study published recently by Herzog et al. [45], analyzing 406 tests in 166 patients, the findings supported the utility of defining different phenotypes according to expiratory peak-flow fall, as this phenotypes can have a beneficial impact on treatment selection.

In standard practice at our center, all candidates for lung volume reduction undergo a bronchoscopy that includes Chartis system assessment. In addition to the collateral ventilation study, a standard bronchoscopy is performed prior to the procedure providing anatomical information of the patient airway and allowing for biopsy-sample acquisition with a view to ruling out microorganism colonization.

We have recently begun using VIDA software (VIDA Diagnostics Inc., Cupertino, USA) in correlation with Chartis analysis in selected cases. If the observations from previous studies are confirmed [46], novel emphysema-quantification software may render Chartis assessment unnecessary in certain cases, leading to a reduction in costs. In spite of the advantages of this method, we believe that performing a bronchoscopy prior to the treatment provides relevant information.

Certain groups exist in which decision-making should be based on CT-scan findings. In cases with more than 90 % of visible lung fissure, these are ancillary to endobronchial-valve treatment. In those where less than 75 % of fissure is seen, coils treatment would be the best option. Finally, for patients with visible fissure between 75 and 90 %, a Chartis system assessment is recommended to support the final decision on treatment approach.

Pulmonary circulation assessment

Pulmonary hypertension is common in long evolution COPD; patients presenting long-standing COPD are classified as group 3 according to the NICE classification [47]. In endoscopic lung volume reduction, pulmonary artery pressure (PAP) values over 50 mmHg measured by transthoracic echocardiography contraindicate coil treatment.

Regarding this circumstance, Eberhardt et al. [21] recently published a pilot study with six patients diagnosed with pulmonary hypertension who underwent to lung volume reduction with endobronchial valves. In the study, right heart catheterization was done before and 90 days after the procedure,

leading to an improvement in hemodynamic and functional parameters in five out of six patients.

This study parts from standard clinical practice by performing right heart catheterization (the gold standard for pulmonary hypertension diagnosis) for patient assessment. Right heart catheterization is essential to the trial because the main outcome is to measure hemodynamic values. However, this is an invasive procedure which cannot be used in all patients.

Despite the special considerations required for emphysematous patients (bad echographic window), transthoracic echocardiogram has proven to be a non-invasive method which provides important information for estimating pulmonary circulation parameters.

Rehabilitation program

Rehabilitation programs are a very important component of COPD treatment, since respiratory musculature upkeeping may bring about an improvement in symptoms and functional reserve. All actions should be accompanied by optimal bronchodilator treatment requiring good patient compliance and familiarity on the part of the patient.

Furthermore, motor rehabilitation is also very important since, in several cases, these patients suffer from a substantial muscular atrophy with a multifactorial etiology (iatrogenic, lack of training). Prior to the procedure, patients must learn how to follow an exercise program and perform it daily to the extent that they are able to tolerate, as doing so will keep them in the best possible physical condition before the procedure.

In several cases, symptomatic improvement is produced in a relatively short period of time after the procedure (especially in coil treatment) This window of time provides a good opportunity to stress the importance of daily physical activity, especially since patients tend to be most motivated at this point.

Improved exercise tolerance after lung volume reduction was evidenced in a publication by Faisal et al. [48]. This study compared the results achieved in an exercise test conducted using a cycloergometer both before and after the treatment, in two groups of patients which the authors named "effective treatment" (higher than 350-cm^3 reduction in RV) and "control group" (non-responders and placebo-treatment patients).

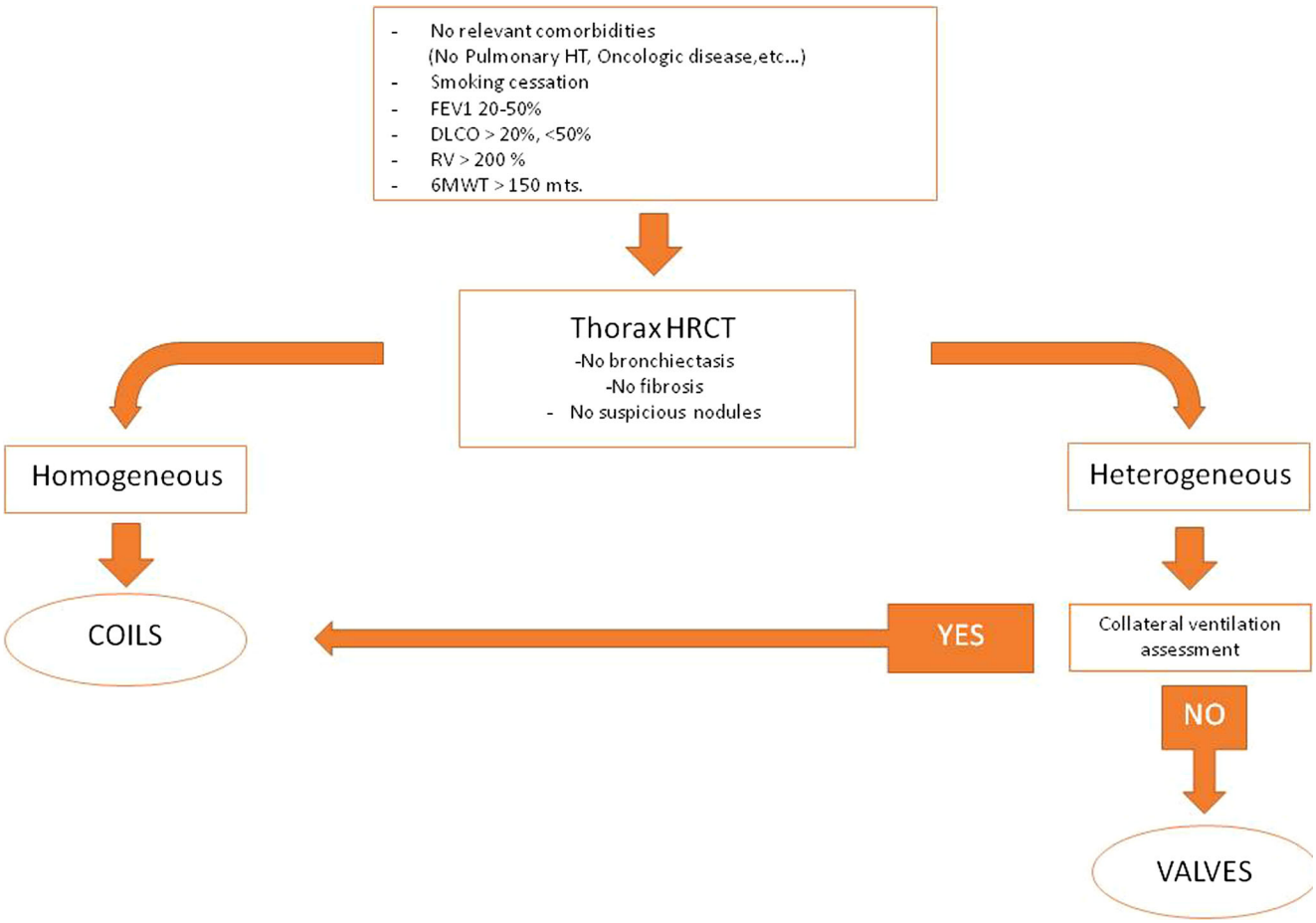

Fig. 1 Simplified decision-making tree for endoscopic lung volume reduction treatment selection

Other considerations to be taken into account

In patients with alpha-1 antitrypsin deficiency lung volume reduction treatment with endobronchial valves can be administered as compassionate use and outside of clinical trials. In our experience, with two patients treated, we have noted a remarkable improvement in symptoms and quality of life.

Chronic anticoagulant and antiplatelet therapy are considered to be strictly contraindicated for coil placement, although these patients may be candidates for endobronchial valves.

In patients with chronic hypercapnia or those who require ventilation support with BiPAP, lung volume reduction is not considered a therapeutic alternative.

Choosing the optimal management

After performing all diagnostic tests, the choice of which treatment to apply on each patient must be taken by consensus between all the members of the interventional unit.

In general, once a patient meets the inclusion criteria for this treatment, the radiologic findings and collateral ventilation assessment will guide the decision as to which device or technique to use (Fig. 1).

In the event of homogeneous emphysema patients, coil treatment is the most suitable choice, while in heterogeneous distribution of the disease, the decision to choose one over the other will be determined by the results of collateral ventilation assessments.

If available data indicate complete lobar exclusion (assessed by imaging test or through the Chartis system), unilateral valve treatment of the most damaged zone would be the first option, since it has the added advantage of being reversible in case of complications. Due to their characteristics, endobronchial valves allow more flexibility with treatment criteria, and conditions such as anticoagulant therapy or pulmonary hypertension may not represent an obstacle for performance of the procedure.

When there is evidence of collateral ventilation, the best option is to perform bilateral treatment with coils, selecting the most damaged lobes for placement. The most common practice is to place coils in both upper lobes, though the lower lobes may be treated in selected cases.

Conclusions

Endoscopic lung volume reduction is a therapeutic alternative for selected patients, providing increased quality of life and functional improvement with an adequate safety profile. The evidence available supports use of these treatments, although their high costs make it essential an accurate patient selection, done by experienced units and preferably as part of international registries.

Moreover, it is important that all the physicians involved in providing care for respiratory patients are aware of these treatment alternatives. Widespread familiarity with the procedures can increase the number of patients who benefit from these innovative techniques.

These techniques do not preclude lung transplant. Patient meeting all requirements can be included on lung transplant waiting lists, and endoscopic lung volume reduction may even be used as a bridge procedure prior to the surgery.

Compliance with ethical standards

Conflict of interest Iker Fernadnez-Navamuel, Javier Flandes, and Javier Alfayate report having received financial support for research from PneumRx.

Human and animal rights and informed consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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