

Bronchoscopic lung volume reduction in advanced pulmonary emphysema: the safety and efficacy of novel methods

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SUMMARY. Large multicentre studies have shown the effectiveness of lung volume reduction surgery (LVRS) in improving functional parameters and exercise tolerance in selected patients with severe pulmonary emphysema of upper lobe predominance. A number of bronchoscopic techniques have been developed under the term "bronchoscopic lung volume reduction" (BLVR), which aim to lower the complications and cost of LVRS. These include airway bypass by creation of airway/parenchyma communications under ultrasound (US) guidance, the use of one-way endobronchial valves and endobronchial coils, hot vapour ablation, and "biological" lung volume reduction through alveolar filling with polymer material. These methods are generally simple and safe, with a favourable complications profile, and they require less infrastructure and interventional experience than the open surgical approach. Airway bypass, although effective and relatively safe, does not provide lasting effects. The use of valves and alveolar filling polymers, in contrast, has been shown to produce sustainable improvement of exercise tolerance and quality of life (QoL). Alveolar filling, at the cost of being non-reversible, presents advantages regarding spirometry values, QoL, exercise tolerance and dyspnoea, not only in patients with heterogeneous upper lobe emphysema, but also in patients with homogeneous emphysema, in whom most of the other bronchoscopic or surgical procedures are not indicated. Coils and vapour ablation still need more extensive research to validate their clinical effectiveness. To date, the research data on the effectiveness of BLVR are not yet considered to provide sufficient evidence for official therapeutic recommendations of their use to be launched by the regulating authorities. The cost/effectiveness issue is also under evaluation. New, more extensive multicentre studies are underway which aim at better selection and stratification of patients in order to further evaluate the safety and effectiveness of these techniques, before wider use of this revolutionary approach for severe lung emphysema can be advocated. *Pneumon* 2012, 25(1):35-49.

INTRODUCTION

Bronchoscopic lung volume reduction (BLVR) is the main non-surgical approach to the problem of lung hyperinflation in pulmonary emphysema.

Surgical volume reduction of hyperinflated lungs has been shown to decrease hyperinflation, as expressed by the RV/TLC ratio, allowing the remaining healthier part of the lung to expand and restoring lung mechanics, thus improving the difficulty in breathing and the exercise tolerance of patients.¹ This approach was initially proposed by Otto Brantigan in 1959² and additionally explored by Fessler and Permut in 1998.² Several sporadic studies reported during the 1990s confirmed the effectiveness of surgical lung volume reduction in the improvement of both the functional parameters and exercise tolerance for some groups of patients suffering from emphysema³⁻⁵. The findings of these studies have been validated by a large, multicentre, randomized trial, the National Emphysema Treatment Trial (NETT)⁶⁻¹¹.

The NETT study included 1,218 patients with emphysema and compared overall survival and exercise tolerance after optimal standard-of-care treatment (i.e., medication and physical rehabilitation) in those undergoing lung volume reduction surgery (LVRS) and those treated medically only (optimal group)⁸. During the study, an interim analysis was performed, and a number of patients suffering from homogeneous emphysema and severe obstruction [defined as forced expiratory volume in 1 second (FEV₁) ≤20% of the predicted value and diffusing capacity of carbon monoxide of the lung (DLCO <20%)] were excluded. For this group comprising 140 patients, defined as the high risk group, high intrasurgical mortality was observed at 30 days of follow up (16%) along with low benefit from LVRS⁷.

Of the patients suffering from predominantly upper lobe emphysema with low exercise tolerance, those who underwent LVRS, showed improvement at 2-year follow up in exercise tolerance (an increase of <10 Joules), quality of life (QoL) [defined by an 8-point reduction in the St George's Respiratory Questionnaire score (SGRQ)] and overall survival, compared with the patients who received only optimal standard-of-care treatment⁶.

The patients with intermediate characteristics showed modest improvement of exercise capacity, spirometric values, dyspnoea and QoL scores, but no improvement in overall survival, in comparison with the control group¹¹.

Postoperative mortality at 90 days was 7.9% in the LVRS group and 1.3% in the control group. In addition,

the LVRS group demonstrated significant intra-operative morbidity; 59% of the patients suffered major complications, including pneumonia, need for re-intubation and hospitalization in the intensive care unit (ICU) for a period of >2 days, cardiac complications, such as myocardial ischaemia, pulmonary embolism and arrhythmia, and air leakage, which was a complication possibly leading to further surgery⁹. After exclusion of the high risk group, the 90-day mortality in the LVRS group was 5.5%¹³.

Meta-analyses of the 5-year survival data showed a decrease in the risk of death for the group of patients who had an optimal response to treatment and underwent surgery for lung volume reduction as proposed by NETT^{9,13}. Similar results were obtained in earlier series (Table 1)¹⁴.

These relatively encouraging results, combined with relevant health economics analyses¹² have led the regulatory authorities to the formal recommendation of LVRS for patients with unhomogeneous upper lobe predomi-

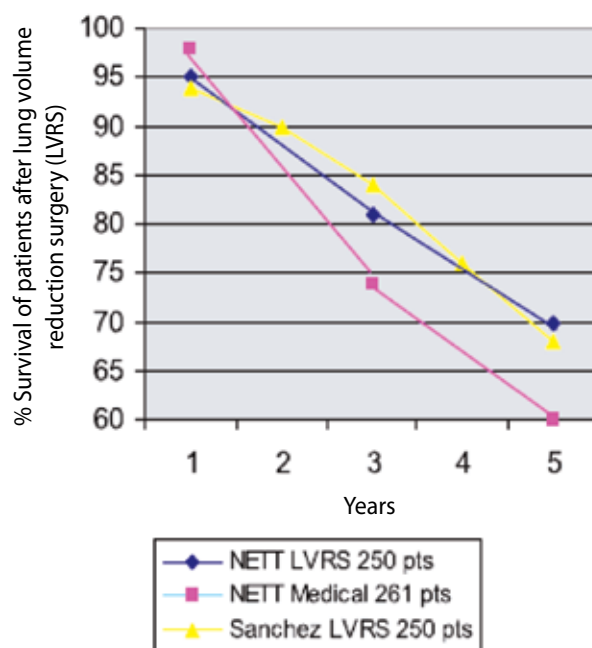


TABLE 1. % Survival of patients after lung volume reduction surgery (LVRS). The curves of 5-year survival in patients with upper lobe emphysema after lung volume reduction surgery (LVRS) (NETT study and observation study by Cicconet et al.) in comparison with the NETT control group. The survival of the patients after LVRS in the NETT study is practically equal with that in the Ciccone et al. study, with better results than the NETT control group, which received only standard medical treatment. (Modified by Berger et al: Lung Volume Reduction Therapies for Advanced Emphysema: An Update. Chest 2010;138:407-417).¹⁴

nance emphysema, low exercise tolerance, preserved FEV₁ and DLCO >20% (i.e., the optimal responders). In spite of the fact that recommendation for reimbursement of the surgical costs for this group of patients was made to the insurance companies, the number of patients who underwent LVRS during the last 5 years was minimal.

Subsequent research was focused on the development of a variety of new bronchoscopic alternatives that would either:

- A) bypass the obstructed small airways by creating collateral (exo-anatomical) routes of ventilation, which could decrease air trapping and expiratory flow limitation
or
- B) decrease lung volume by causing atelectasis of the most diseased part of the lungs, by either the use of endobronchial one-way valves, or injection of biopolymers which would fill the alveoli, or the use of steam, wire stents, etc., all aiming at results similar to those of LVRS.

This review systematically presents the documented evidence of these techniques of BLVR.

A. Airway bypass

This method, initially proposed by P. Macklem, consists of the creation of new exo-anatomical routes for which he coined the term "spiracles". These holes create a channel between the thoracic wall and the pulmonary parenchyma, permitting collateral ventilation from emphysematous lung segments and through which trapped air exits because of the lower resistance.¹⁵ This approach had several acceptance issues.

A pioneering endoscopic modification of this method by Cooper¹⁵ demonstrated that the creation of holes in peripheral bronchi which communicate with the parenchyma reduces the resistance in expiratory flow, leading to an effective reduction of air trapping. In theory, this model could be used not only in upper lobe emphysema, as in LVRS, but also in homogeneous emphysema.

Holes were opened in bronchi by radiofrequency ablation, which led to the adjacent parenchyma, and stents were placed *ex vivo* to keep them open.¹⁶ FEV₁ measured before and after the procedure showed significant increase (median values 245 +/- 107 ml before and 447 +/- 199 ml after the creation of three routes, and 666 +/- 284 ml with six routes), establishing in this way the experimental basis for further research.¹⁶ The next step in the evolution of this method was the use of an endoscopic Doppler catheter (Bronchus Technologies Inc, MountainView, CA, USA) for

the detection and avoidance of vessels, thus allowing safe creation of holes in the bronchial wall.

The ensuing study by Rendina et al¹⁷ established the safety of bronchial wall puncturing after detection of vessels by the Doppler catheter in patients who were planned for lobectomy. The major complications were bleeding (≤ 20 mL) and less often, pneumothorax.

Later studies showed that these newly opened routes became progressively obstructed after 2-3 weeks, while the use of stents expanded their life for only a limited time. For this reason, a chemotherapeutic agent, Mitomycin C was used to line the stents to prevent development of scar tissue within the lumen and thus obstruction of the route.¹⁸

Shortly after this, a new method of hole opening was developed, using a TBNA needle with a built-in expansion balloon, and new stents coated with Paclitaxel, also a chemotherapeutic agent.¹⁹

Cardoso and colleagues¹⁹ studied 35 patients, mainly with homogeneous emphysema, who underwent this new method, in order to evaluate its safety and effectiveness in terms of spirometry, dyspnoea, QoL and 6-minute-walk-test (6MWT). One death occurred during the procedure, and other complications reported were pneumomediastinum (5.3%), exacerbation of chronic obstructive pulmonary disease (COPD) (38%), lower respiratory tract infection (27%), and unstable angina (2.7%). The bronchoscopic follow-up of the patients showed successful conservation of the channel patency at 6 months in 69% of patients. It was demonstrated that patients with higher hyperinflation (expressed by the RV/TLC ratio) had a RV decrease of 1,040 mL (-16.2%, $p = 0.001$) at one month of follow up and 870 mL (-4%, $p = 0.022$) at 6 months. In the low hyperinflation group no statistical difference was detected at 6 months. The authors emphasize that increased hyperinflation was a determinant of achieving statistically significant differences between patient groups.

The randomized trial of airway bypass in homogeneous emphysema (EASE)²⁰, the most recent, multicentre, randomized study examining this method, included mainly patients with homogeneous emphysema. The TBNA method with a built-in dilatation air chamber was used for opening holes in the bronchial wall, under endoscopic Doppler guidance to choose a correct location away from vessels. After opening the routes, Paclitaxel coated stents were placed to avoid occlusion (Figure 1).

Of the 305 patients who were enrolled, 208 received treatment and 107 were included in the control group and underwent sham bronchoscopy - stent placement.

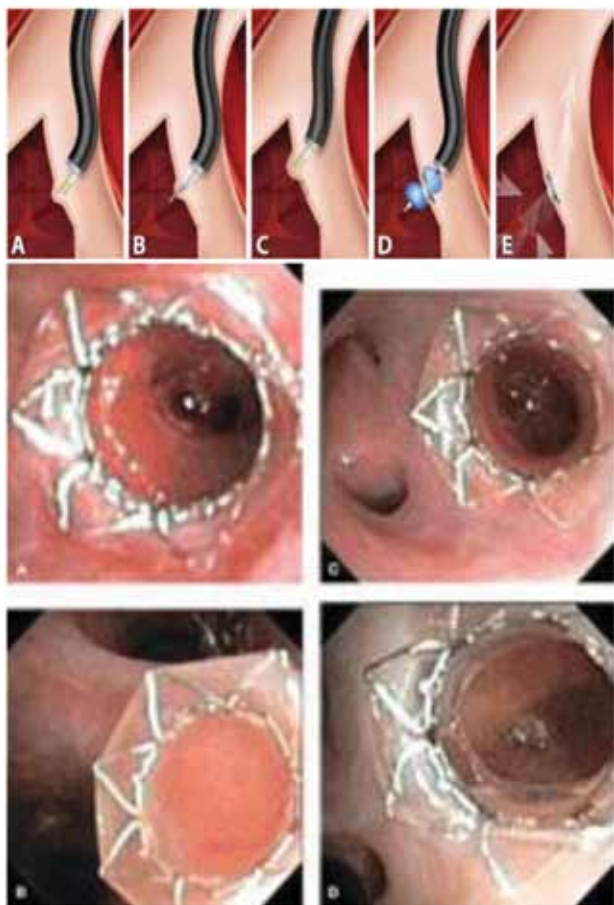


FIGURE 1. Bronchial bypass method with hole opening (EASE trial). A TBNA needle is used with guidance by endoscopic Doppler in order to avoid neighbouring vessels when choosing the target. The needle has a built-in dilatation chamber.

The inclusion criteria were homogeneous emphysema, as defined by chest high resolution computed tomography (HRCT), $FEV_1/FVC \leq 70\%$, $RV/TLC \geq 0.65$, $RV > 180\%$ predicted, and participation in rehabilitation programme for ≥ 6 weeks. Exclusion criteria were FEV_1 reversibility > 200 ml, $DLCO < 15\%$ predicted, body mass index (BMI) > 31 , COPD infectious exacerbations (3 or more in the last 12 months) and pulmonary hypertension.

The primary end points were safety, FVC increase by 12% and RV decrease. The first results, announced in an oral presentation at the European Respiratory Society (ERS) in 2010²⁰, demonstrated the safety of the method. Severe complications occurred in 3% of the the treatment group (one death, one episode of severe haemoptysis, two episodes of pneumothorax, lower respiratory tract infection in two patients and respiratory failure with

need for mechanical ventilatory support in one patient). Improvement in the primary end points and FEV_1 improvement were statistically significant on the first day of measurement after treatment, but did not persist after 3 or 6 months. Dyspnoea, estimated by the MMRC scale, did not show statistically significant difference between the two groups. Chest HRCT scan showed an initial decrease in lobar volume by 89% in the treated patients, but subsequent volume increase by 56% at 6 months, at which time only 24% of the routes were still patent. Obstruction of the channels is the most probable explanation for the reversal of the provisional improvement after 3 and 6 months.

B. Bronchoscopic lung volume reduction

1) Endobronchial valves

Initial studies were performed by Sabanathan and co-workers²¹ of peripheral bronchi exclusion in emphysematous regions of the lung with the use of endobronchial wedges, made with a metal frame and biocompatible sponge. Their study enrolled a small number of patients who showed an improvement in dyspnoea, exercise tolerance and QoL.

The use of one-way endobronchial valves in emphysematous regions of the lungs aimed at inducing atelectasis in these regions, reducing hyperexpansion and possibly providing symptomatic relief. These devices allow expiratory airflow and the excretion of mucus, but do not allow inflow of air into the specific bronchus, thus leading to post-obstructive atelectasis of the chosen pulmonary segment. Reversibility of atelectasis, if deemed necessary, by valve removal is an important advantage of this method. The most recent clinical studies examining the two basic types of these newly developed valves are reviewed below.

IBC umbrella valve (Spiration Inc. Redmond USA)

The IBC umbrella valve is placed through the flexible bronchoscope. It consists of a covered framework of Nitinol (a nickel and titanium alloy, which possesses thermal memory and reshapes to its previous form when introduced into the airway and exposed to body temperature). It carries umbrella-shaped hooks which hold the valve in position without damaging the airway, and it is covered by a synthetic polymer (Figure 2). The valve allows a one-way flow of mucus and air and inhibits air inhalation into the treated segmental bronchus. As it is radio-opaque its position can be easily identified by chest



FIGURE 2. IBV^a umbrella (Spiration Inc., Redmond USA). The valve consists of a Nitinol framework covered by a synthetic polymer with umbrella-shaped hooks which hold the valve in position without damaging the airway. In theory, it allows exhalation and mucus outflow from the bronchus where it is placed, without allowing air entrance, thus gradually causing atelectasis of the specific distal lung segment.

X-ray. A central spike allows bronchoscopic removal of the valve when necessary.

Several clinical studies have examined the improvement in various spirometric, clinical and radiological parameters of patients with emphysema treated by these valves.

In a multicentre study published in 2007,²² the course of 30 patients with emphysema of upper lobe predominance and severe or very severe obstructive syndrome was assessed. This study confirmed the safety of the method; the valves, which were placed unilaterally in the upper lobes were well tolerated by patients without any serious complications. The rates of infection, pneumonia and COPD exacerbations were low. In a follow-up period of 30 days after valve placement, the most frequent adverse reactions were COPD exacerbation (6%), pneumonia (6%), haemoptysis (1%), chest pain (3%) and dyspnoea (4%). The majority of patients were followed for at least 6 months after valve placement.

The study did not show significant improvement in spirometry (as evaluated by FEV₁), but there was improvement in QoL, estimated by SGRQ at 1, 3 and 6 months compared to the baseline measurements, with a decrease in the overall score by -6.8 +/- 14.3 points. The authors comment that the perceived improvement in QoL may be due to the decrease of dynamic hyperinflation, which can improve exercise tolerance without affecting spirometric parameters at rest.

In a multicentre study²³ that enrolled 57 patients with emphysema, also of upper lobe predominance, the lung volume was estimated by chest HRCT before and after placement of Spiration valves, and correlation was made

with spirometric values. The spirometric values were not significantly altered by the treatment, but a volume redistribution was achieved, specifically reduction in the upper lobe volume treated by the valves (i.e., 335 +/- 444 ml in 88% of measurements or 10.2% decrease in 6 months), volume increase in the healthier lower lobes (11.6% increase), and upward migration of the interlobar fissure. A statistically significant improvement in QoL was observed (SGRQ reduction of -8.95 +/- 16.22 at 6 months after treatment). The safety profile was acceptable as only 4 episodes of pneumothorax were recorded and 2 episodes of bronchospasm, and there were no deaths. The authors comment that the improvement in the QoL of these patients can be attributed to the lung volume redistribution towards the healthier areas of the lungs, without reduction of the total lung volume.

A recent multicentre study²⁴ on 91 patients with upper lobe emphysema examined the safety and efficacy of the Spiration valve placement. No deaths occurred during valve installation, but regarding adverse reactions, 11 patients (12.1%) suffered pneumothorax during the 12-month follow-up, -one of whom developed tension pneumothorax 4 days after installation of the valve that ultimately led to his death. Some cases of pneumonia were also recorded in the region of the valve (2.2%), but there was no further pneumonia episode during the first 3 months of follow up after the valve placement.

Regarding efficacy, the study showed a statistically significant improvement in QoL, as shown by a 4 point decrease on the SGRQ scale (-5.2 +/-12.3 after the 1st month, -5.1 +/-15.2 at 3months, -8.2 +/-16.2 at 6 months and -9.5 +/-14.4 at 12 months follow up). The authors comment that this improvement was correlated with a ≥10% increase in volume of the healthier lower lobes in 75% of patients, as estimated by chest HRCT. This correlation was attributed to possible improvement in the ventilation-perfusion ratio after treatment. No statistically significant improvement was observed in the spirometric parameters or the 6MWT.

It was concluded that FEV₁ and 6MWT may not be able to quantify benefits derived from this particular treatment, which are reflected by SGRQ and the statistically significant correlations with lung volume shifts on chest HRCT. Valve skeptics argue that the patients' psychological background may play an important role in perceived changes in QoL (placebo effect).

Zephyr valve (PulmonX^a Redwoodcity, CA, USA)

The Zephyr valve (PulmonX^a Redwoodcity, CA, USA)

has been studied extensively in clinical trials. It is composed of a nitinol framework with an internal one-way valve mechanism like a "duck beak" made of silicone, and is available in 2 sizes. (Figure 3)

The valve is introduced bronchoscopically after measurement of the exact diameter of the airway.²⁵ The position of the valve can be located by chest X-ray.

Following the satisfactory completion of the emphysematous animal model studies, many clinical studies followed, both multicentre and single centre, and to date a total of more than 100 patients have been enrolled. The enrollment criteria were usually those defined by the NETT study, namely upper lobe emphysema, FEV₁<30%, DLCO>20%, absence of pulmonary hypertension and hypercapnia. Most of the selected patients were suffering from upper lobe emphysema, thus having a lesser degree of collateral ventilation and, as a result, they had the potential for success in producing lung volume reduction and atelectasis.²⁶ The first clinical study of the Zephyr valve, conducted in 10 patients, demonstrated the safety of the method²⁷, but subsequent studies showed significant heterogeneity in their results. In certain patient series, notable improvement in clinical parameters was observed, in particular in the dyspnoea and QoL scores²⁸. In other series, improvement in symptoms and QoL of life is documented, along with enhancement of the spirometric values (RV, inspiratory capacity, VC +/- FEV1).²⁸

A multicentre study²⁹ of 98 patients confirmed the safety of the method, since serious complications occurred in only 8.2% of patients – mainly pneumothorax, pneumonia and COPD exacerbation. Small improvements in spirometric parameters were shown on the 90th day of follow-up; FEV₁ increased by 10.7 +/- 26.2% (p= 0.007)

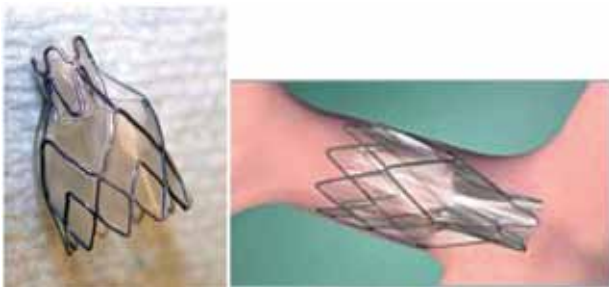


FIGURE 3. EBV- Zephyr valve (PulmonX³ Redwoodcity, CA, USA). The valve consists of a Nitinol framework with an internal one-way valvular mechanism in the shape of a «duck beak» made of silicone. It is placed via bronchoscope after precise measurement of the airway diameter. It can be identified by chest X-ray after its placement.

and FVC by 9.0 +/- 23.9% (p = 0.024), with a decrease of RV by 4.9 +/- 17.4% (p = 0.025). Finally, 6MWT showed a small improvement by 23 +/- 55.3% (p = 0.001). Certain individual studies showed a statistically greater benefit for patients with low FEV₁ and high RV at baseline, and those who underwent unilateral, complete exclusion of the upper lobe, compared with those who underwent bilateral, incomplete exclusion.

The findings of the most important multicentre, randomized trial investigating this method, the Randomized Study of Endobronchial Valves for Advanced Emphysema (VENT Study) were published recently.³⁰ In this study, 321 patients with upper lobe emphysema were randomized, 220 receiving Zephyr valves (the valve group) and 101 serving as the control group. The patients were enrolled according to the NETT study criteria and before randomization they all received standard treatment with medication and physical rehabilitation for 8 weeks.

The primary endpoints of the study were FEV₁ and 6MWT changes, and the secondary endpoints were improvement in QoL (assessed by SGRQ) and dyspnoea (MMRC scale) at 6 months follow up. The safety of the method was also evaluated at 6 months, including deaths and possible adverse reactions, such as empyema, massive haemoptysis, post-obstructive pneumonitis due to the valves, pneumothorax and respiratory insufficiency requiring mechanical ventilation. In addition, the presence of radiologically complete interlobar fissure (>90% of the fissure present on chest CT) was investigated, since this is correlated with the presence of collateral ventilation between lobes. The valves were placed by flexible bronchoscope or by a combination of flexible and rigid bronchoscope. Local (71.5%) or general (28.5%) anaesthesia was used, and the valves were placed in segmental or subsegmental bronchi, aiming at isolation of the target lobe.

The frequency of significant adverse reactions during the 6 months of follow-up was 6.1% in the valve group and 1.2% in the control group, which did not surpass the predicted safety criteria described in the study plan. At 12 months, the frequency of adverse reactions was similar in the two groups. In the valve group, the 6 deaths (2.8%) reported during the first 6 months were due to respiratory insufficiency (irrelevant to the procedure), cancer, ischaemic colitis and haemoptysis, while no deaths occurred in the control group. At 12 months, the mortality was similar in the 2 groups. The most common adverse reactions in the first 90 days were COPD exacerbation (7.9%), haemoptysis (5.6%) and pneumothorax (4.2%).

During long-term follow up, the most frequent complication was pneumonia involving the occluded lobes, presented by 9 patients (4.2%), in 6 of whom the valves had to be removed. Episodes of haemoptysis were more frequent (6.1%) in the valve group.

In the primary endpoint analysis, the valve group showed a slight increase in FEV₁ (4.3%) at 6 months of follow-up, while the control group showed a decrease of 2.5%. The median difference (6.8%) between two groups was statistically significant ($p = 0.005$).

Similar results were noted for 6MWT: a slight increase of the walking distance (2.5%) was observed for the valve group and a decrease (3.2%) for the control group at the 6 month follow up, and the median difference, 5.8%, was also statistically significant ($p = 0.04$). Finally, no statistically significant improvement was detected in the secondary endpoints: QoL (evaluated by SGRQ), exercise tolerance (measured by ergometry) and the MMRC dyspnoea scale.

The subgroup analyses of the study demonstrated that increased emphysema heterogeneity (as defined by chest HRCT), anatomically complete interlobar fissure, successful obstruction of the valve-treated bronchus, and the absence of collateral ventilation comprise prognostic factors for significant improvement in FEV₁ and 6MWT. For patients with complete interlobar fissure, FEV₁ improvement was significant (16.2% in 6 months), but 6MWT did not differ significantly between the groups. In patients with greater emphysema heterogeneity the improvement in FEV₁ and 6MWT was significant (10.7%; $p = 0.004$, and 12.4%; $p = 0.002$, respectively). The patients treated with valves showed significant decrease in target lobe volume after 6 months, as measured by chest HRCT (378.4ml vs 16.3ml in the control group; $p = 0.002$). This decrease was more pronounced (712.5ml) in the group with complete interlobar fissures. The characteristics of the cohort analysis defined a phenotype for the emphysema patients who are likely to show a significant response to treatment with Zephyr endobronchial valves, to be confirmed in future studies.

In order to target patients in whom complete exclusion of the upper lobes is possible, the Chartis^o system was developed, which detects the presence of collateral ventilation between lobes. The system consists of a catheter which is introduced through the flexible bronchoscope to measure flow and pressure inside the airway. This system was evaluated for safety and effectiveness with regard to the prediction of collateral ventilation in 25 patients with endobronchial valves.³¹ The method was found to be safe, as only one patient suffered from pneumothorax, but in 4

others, it was not possible to measure pressure, flow and pulmonary resistance values for technical reasons. In the remaining 20 patients, the measured values predicted atelectasis after valve placement, detected on chest X-ray in 18 (90% of the total), while in 2 patients (10%), there was discordance between measured values and X-ray findings. Two further studies on this system^{32,33} involving a small number of patients were presented at ATS 2010e, which confirmed these findings, but larger, randomized trials will be necessary for validating this method for use in everyday clinical practice.

2) Wire coils – airway implants

Another method of endoscopic lung volume reduction indicated for patients with heterogeneous emphysema is the PneumRx^o coil (MountainviewCA, USA) (Figure 4). These coils are made of nitinol alloy and when deployed they compress and “strangle” the airway and the adjacent parenchyma, causing atelectasis of the «target lobe». On the average, 10 coils are placed in the targeted lobe in order to achieve volume reduction. The advantage of this method is the possibility of removal of the coils. The initial safety results of the method, derived from studies that enrolled 6 patients in total, showed an increased incidence of pneumothorax and obstructive pneumonitis, and also coil migration.³⁴⁻³⁶

In these studies, bilateral lung volume reduction was performed, in two bronchoscopic sessions with a time interval of 3 months. The greatest decrease in lung volume was achieved at the 2nd and 4th weeks after placement. Spirometry parameters and exercise tolerance and QoL questionnaires all showed a trend for improvement. Larger, randomized trials are necessary for confirmation of these first observations and investigation of the safety. To date

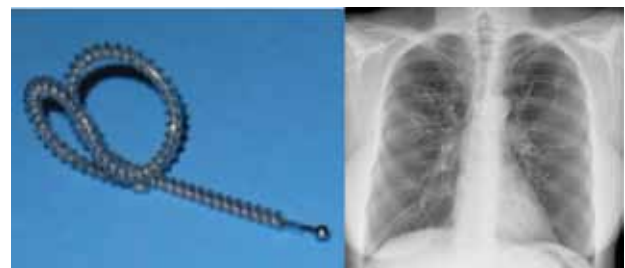


FIGURE 4. Pulmonary coils PneumRx³ (MountainviewCA, USA). The coils are made of Nitinol, and they expand and compress-strangle the airway and the parenchyma, resulting in atelectasis of the target lobe. On average, 10 coils are placed in the affected lobe in order to achieve lung volume reduction.

most data on this technique are derived from anecdotal studies presented during International Congresses, and are reported in this review with reservation.

Safety and effectiveness of this method were examined in 16 patients with heterogeneous emphysema and low FEV₁ (28% of predicted in average)³⁷. An average of 10 coils per person was placed, unilaterally in 5 patients and bilaterally in 11 patients, in 2 sessions. The adverse reactions during 30 days of follow-up were: pneumothorax (1), pneumonia (1), COPD exacerbation (7), and haemoptysis <5mL (15), all of which were managed effectively. The results were encouraging, as the placement of the coils in one lung resulted a statistically significant improvement of the parameters at follow-up, in comparison to the initial values: Δ FEV₁ +9.2% \pm 4.9%, Δ FVC +8.7% \pm 5.0%, Δ RV -7.5% \pm 2.6%, Δ 6MWT +28.8% \pm 9.5%, Δ mMRC -0.8 \pm 0.4, and Δ SGRQ -13.1 \pm 4.0. The second placement of coils led to further, statistically significant, improvement of the parameters: Δ FEV₁ +19.9% \pm 7.1%, Δ FVC +13.0% \pm 3.8%, Δ RV -11.2% \pm 2.8%, Δ 6MWT +35.0% \pm 15.4%, Δ mMRC -1.0 \pm 0.4, and Δ SGRQ -14.5 degrees \pm 4.0.

In another study,³⁸ the patient choice for placing the coils was based on quantitative analyses of the density of pulmonary parenchyma on chest HRCT. The changes were estimated in 6MWT, pulmonary function tests and SGRQ between measurements before and those made one month after treatment. These changes were compared with the quantitative measurements from the chest HRCT before treatment.

Statistically significant correlation was demonstrated of the parenchymal density after coil placement, with changes in 6MWT ($p=0.016$), FVC ($p=0.012$), RV ($p=0.001$) and RV/TLC ratio ($p=0.001$), but not with changes in FEV₁ ($p=0.086$), SGRQ ($p=0.079$) and TLC ($p=0.102$). The authors conclude that pulmonary parenchymal density measurement may become a useful tool for the selection of patients for coil placement.

The same group of investigators addressed the safety of this method³⁹ in 11 patients with homogeneous and heterogeneous emphysema, who underwent coil placement under general anaesthesia. Adverse reactions were reported in 11 patients with disease of mild (33%) or moderate (64%) severity. The adverse reactions related to treatment were: dyspnoea (10), cough (5), COPD exacerbation (3) and chest pain (1). The improvement in clinical, spirometry and quality of life parameters in these patients with heterogenous emphysema was statistically significant, although the patient numbers were insufficient for definitive confirmation of this observation.

There have been no reports from large, multicentre trials examining the safety and effectiveness of this method, and thus further investigation is required.

3) Hot vapour ablation

The administration of steam is a new method (BTVA[®], Uptake Medical Corp., Seattle), which is currently being studied in clinical trials after the completion of preclinical animal trials that provided the initial data on efficacy and safety.⁴⁰ The system consists of a steam generator and a bronchoscopic catheter with an airchamber (Figure 5). The catheter is inserted through the bronchoscope, the airchamber is inflated to block the "target" bronchus and an exact quantity of steam is released (10 cal/gr). After the administration of steam, the airways sustain thermal damage (blanching) that leads to a scarring reaction, progressive atelectasis and shrinkage of the pulmonary segment distal to the treated bronchus.

The first pilot study⁴¹ on 11 patients with upper lobe emphysema demonstrated an acceptable safety profile for this method. The most common adverse reactions

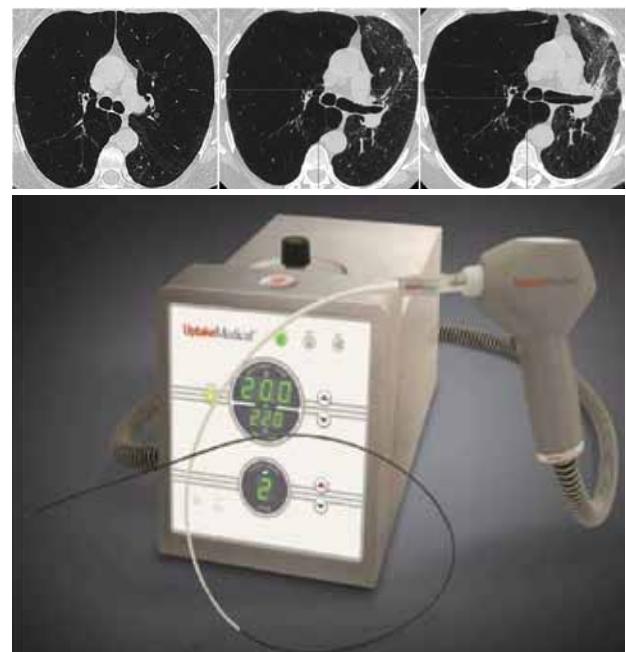


FIGURE 5. (BTVA[®], Uptake Medical Corp. Seattle). The system consists of a steam generator and a bronchoscopic catheter with an air chamber, by which steam is released in a certain dosage (10 cal/g). After the administration of steam the airways present blanching (thermal damage) which leads to a scarring reaction, progressive atelectasis and shrinking of the specific pulmonary segment.

were pneumonia and COPD exacerbation. Steam was administered, unilaterally, to patients with the following criteria: FEV₁ 32% of predicted, RV 219% of predicted and DLCO 34% of predicted. The results demonstrated no change in FEV₁ at 6 months follow-up, but improvements in DLCO (38% of predicted), Medical Council Dyspnoea Score (2.6 to 2.1) and SGRQ (64.4 to 49.1), and a similar study showed comparable results in 20 patients with heterogeneous emphysema.⁴²

In another recent study⁴³ of 11 patients with upper lobe emphysema, steam was administered unilaterally, and spirometry parameters, QoL (SGRQ) and 6MWT were evaluated at 3 and 6 months. After treatment, a volume decrease of the treated lobe by at least 10% was demonstrated in 10 of the 11 patients. The subgroup of patients with larger heterogeneity of the parenchyma between upper and lower lobes showed a greater improvement in FEV₁ (Δ FEV₁, % 16.3 ± 25.3 vs. 9.0 ± 24.7 in the total number of patients). The 6MWT was significantly improved in the patients with greater heterogeneity, while the SGRQ score improved in both groups. Finally, an acceptable safety profile was established. Larger, randomized trials need to be performed in order to further validate these observations.

4) Alveolar filling method: «Biological» lung volume reduction with BioLVR - AeriSeal® system

"Biological" lung volume reduction is a method based on the administration of a Biological gel (BioLVR) or chemical foam (AeriSeal®, AerisTherapeutics, Woburn, MA) at the alveolar level, producing atelectasis of the "target" lobe. The first generation of sealant used was a combination of fibrin, thrombin, poly-L-lysine and chondroitin sulphate. After failure of this method to gain FDA approval, the second generation of hydrogel was developed, consisting of polyvinylalcohol and pentane, which polymerize immediately after mixing. These two substances are administered by a catheter through the bronchoscope which has been wedged in the selected subsegmental bronchus (Figure 6).

The administration of gel leads to atelectasis resulting in lung volume reduction within 3-6 weeks, independent of the presence or absence of collateral ventilation. The safety of the method, the resultant changes in the spirometry parameters (lung volume, pulmonary diffusion) and the histopathological changes in the lung tissue were examined in emphysema animal models and clinical studies.⁴⁴ Clinical trials of the first generation gel were conducted not only in patients with upper lobe

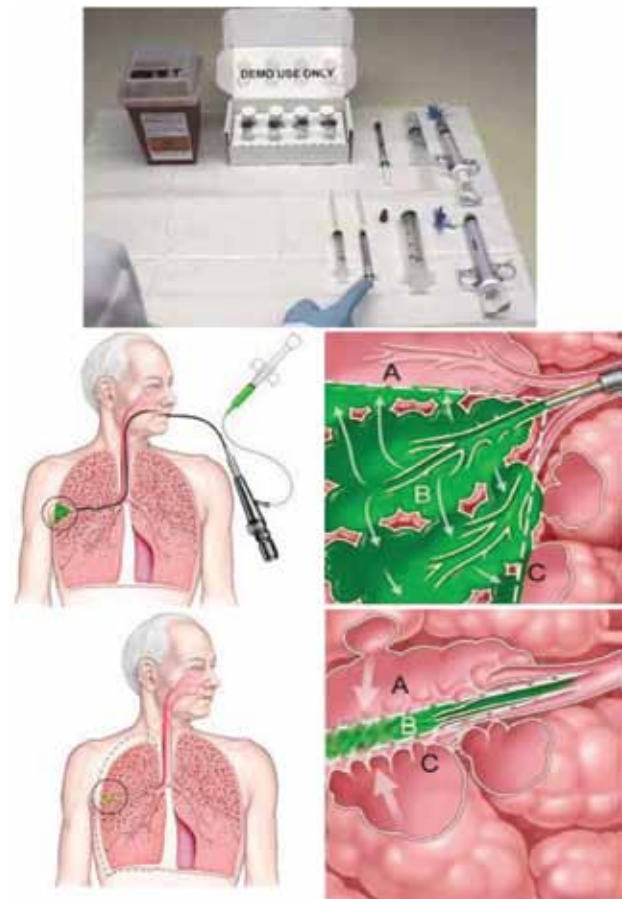


FIGURE 6. Alveolar filling method (AeriSeal[®], AerisTherapeutics, Woburn, MA). "Biological" volume reduction is a method based on the administration of biological gel (BioLVR) or chemical foam (AeriSeal[®], AerisTherapeutics, Woburn, MA) at alveolar level, leading to atelectasis of the target lobe within a period of 3-6 weeks, independent of the presence or absence of collateral ventilation. The instillation is performed by a catheter placed through the bronchoscope which has been wedged in a subsegmental bronchus.

emphysema patients, but also in those with homogeneous emphysema for whom there was practically no other proposed therapeutic solution. The multicentre study of Criner and colleagues⁴⁵ enrolled 50 patients, who received BioLVR in 8 subsegmental lobes of the most damaged parts of their lung, as demonstrated on HRCT, at 2 dosages: either 20ml or 10ml per administration. The results as regards the safety of the procedure were encouraging; all patients tolerated the procedure well, and the most frequent complication was a transient inflammatory reaction (leukocytosis, with fever for 8-24 hours) in 22/25 patients treated with the 10 ml dose and 20/22 patients treated with the 20 ml dose. A significant

number of patients had COPD exacerbation, 5/28 with the low and 9/22 with the high dose. There had been no deaths at 3 month follow-up.

The primary end point of this study, for both dosage schemes, was the statistically significant decrease of the hyperexpansion index RV/TLC, measured at 3 month follow-up. At 6 weeks after administration, patients in both dosage schemes showed a significant increase in FEV₁ and FVC, decrease in RV/TLC and in dyspnoea (MRC and BDI/TDI scales), and improvement in QoL [according to the health related QoL (HRQOL) scale]. At 3 months, these improvements were constant for both groups. The diffusion capacity (DLCO) did not change significantly. At 6 month follow-up, the FEV₁ difference remained statistically significant and had improved in the low dose group; but the FVC, RV and RV/TLC improvements were not statistically significant in this group, but they had remained significant in the high dose group. The average improvement in FEV₁ at 6 months after treatment in the high dose group was 15.6 ± 16.8% in comparison to 6.7 ± 12.9% for the low dose group (p=0.07).

Chest HRCT showed scarring of tissue in the segments where the gel was applied, without any other parenchymal, pleural or mediastinal pathology. After 6 weeks, scar tissue was observed in 57±17% of the low dose treated segments and 68±20% of the high dose treated segments. The number of the segments with scar tissue after 6 weeks was statistically correlated with FEV₁ improvement in both the low (p=0.05) and high (p=0.015) dose groups. This correlation was maintained for 6 weeks in the high but not the low dose group.

The authors conclude that the method presents an accepted safety profile when administering 20 mL of BioLVR per segment, while providing significant initial and long-term positive results, with no increase in adverse reactions.

The same investigators, in a recent multicentre, phase II study⁴⁶ examined a group of 25 patients with homogeneous emphysema, who are usually not selected as candidates for surgical or endoscopic lung volume reduction. The patients were administered BioLVR into 8 subsegmental bronchi in the most damaged parts of the lungs as assessed on chest HRCT, in a dose of 10 or 20ml. The primary end point of the study was the RV/TLC ratio, measured at 3 months after treatment. Efficacy was also measured by changes in FEV₁ and FVC after bronchodilation, DLCO, 6MWT, quality of life (SGRQ) and RV/TLC reduction, 6 months after treatment. The safety of the method was examined, based on possible serious

complications such as death, pneumothorax, empyema, pulmonary embolism, pulmonary abscess, coronary ischaemia, etc. The results, in terms of safety, were encouraging; all the patients tolerated the treatment well, and the most usual complication was a transient inflammatory reaction (leukocytosis and fever lasting 8-24 hours), as observed in the earlier studies, while 2/8 low dose patients and 3/17 high dose patients suffered COPD exacerbations. Chest HRCT follow-up at 6 weeks showed an obvious scarring reaction of 47% (±19%) in the low dose patients and 60% (±20%) in the high dose patients. Δ FEV₁ in the high dose group was +11.6±16.36 (p = 0.007) at 3 months and 13.8 ± 20.26 (p = 0.007) at 6 months. Δ RT/TLC in the high dose group was -6.9 ± 9.6 (p = 0.008) at 3 months but not statistically significant after 6 months. That the number of the scar sites was statistically significantly correlated with FEV₁ increase. Finally, statistically significant improvement in dyspnoea was reported in the high dose group (Δ MRC -0.9±0.93 at 3 months, and -0.8±0.73 at 6 months: p = 0.001) and in SGRQ.

The second generation biopolymeric substance, Aeri-seal, was initially tested in cell culture and animal studies, in order to prove its safety, following which studies were conducted in patients with upper lobe emphysema, but also in patients with homogeneous emphysema.

The treatment escalation study⁴⁷ was an open label, multicentre trial with no control group in which 25 patients with upper lobe emphysema were enrolled, 14 with stage III and 11 with stage IV disease. Biopolymer instillation was performed in 2 sessions, with a 12-week period between sessions, in a total of 12 subsegmental bronchi. The primary end point was the RV/TLC ratio, used as a hyperinflation index, measured at 3 months after treatment. Secondary end points were changes in FEV₁, FVC, DLCO, 6MWT, MRC, SGRQ, measured at 3 and 6 month follow-up.

Regarding the safety of the method, the patients experienced a flu-like syndrome which resolved after 3-7 days, and 6/14 stage III patients and 4/11 stage IV patients suffered COPD exacerbations.

The study documented a decrease in hyperinflation (RV/TLC Δ=-7.4 ± 10.3%, p = 0.031), a finding which was statistically correlated with the improvement at 6 months in spirometry parameters (FEV₁ +15.9 ± 22.6%, p 0.048, FVC +24.1 ± 22.7%, p = 0.01), QoL (SGRQ -9.9 ± 15.3 units, p = 0.048) and dyspnoea (MRC -1.0 ± 1.04 units, p = 0.013). The improvement in the spirometry and clinical parameters was greater in stage III than in stage IV patients, which was to be expected because of the lower initial values of

FEV₁ and DLCO and the higher RV/TLC ratio in the stage IV group. The criteria for significant response to treatment were: Δ FEV₁³+15%, Δ FVC \geq +15%, Δ MRC \leq - 1 U, Δ 6MWT \geq 50m, Δ SGRQ \leq -8 U. Based on these criteria, the results of treatment in stage GOLD III-IV patients at 3 month follow-up are summarized in Table 1.

The next study with the new Aeriseal[®] compound (confirmation study)⁴⁸ enrolled 56 patients with homogeneous (26) and non-homogeneous (30) emphysema. The initial instillation was performed during one session for each lung and in one subsegmental lobe at a time. Preventive antibiotic and corticosteroid use for 7 days was instituted, in order to avoid the inflammatory reaction observed in earlier studies. Bilateral instillation of Aeriseal[®] was offered to all the patients 12 weeks later. The study endpoints were safety and efficacy, measured by spirometry and clinical parameters (as in the earlier studies described above) at the 12th, 24th and 48th weeks of follow-up. The addition of antibiotic and corticosteroid administration to the protocol succeeded in a significant decrease (60%) in inflammatory reactions and COPD exacerbations compared with the earlier studies.

Regarding efficacy, there was a statistically marginal decrease of hyperinflation (RV/TLC Δ = -6.1 \pm 11.8%, p = 0.06) in patients with upper lobe emphysema who were treated by Aeriseal[®] bilaterally, at 12 weeks. The spirometry parameters improved (FEV₁ +16.3 \pm 30.8%, p 0.05, FVC +11.6 \pm 22.3%, p = 0.05), as did the QoL (SGRQ -8.9 \pm 10.5% units, p = 0.001) but paradoxically dyspnoea (MRC) and 6MWT showed no significant improvement. Finally, no significant response was detected in patients suffering from non-homogeneous emphysema of the lower lobes.

A further study⁴⁹ (single session bilateral treatment) examined in 20 patients with upper lobe emphysema and homogenous emphysema the effects of administration of Aeriseal[®] in 4 subsegmental bilateral bronchi simultaneously during one session by flexible bronchoscope. The primary endpoint was set as decrease in upper lobe

volume, 3 months after treatment. Secondary endpoints were the spirometry and clinical parameters described in previous studies. The treatment duration was relatively short and well accepted by the patients. At 3 months a decrease in hyperinflation (RV/TLC -6.1 \pm 15.5%) was observed, along with spirometric improvements (Δ FEV₁ 31 \pm 32.7%, Δ FVC 13.8 \pm 19.4%). Finally, there were improvements in SGRQ (-11.2 \pm 12.7 U) and MRC (-0.5 \pm 0.78U). Multicentre studies for evaluation of the safety and effects of Aeriseal are in progress, for confirmation and validation of these results in larger groups of patients.⁴⁸

DISCUSSION

Review of the research results on lung volume reduction in emphysema leads to several interesting conclusions:

1. The multicentre surgical trials, of which the NETT study was the most important, have clearly shown that LVRS improves symptoms, spirometry, exercise tolerance and survival in a specific group of patients (i.e., those with upper lobe emphysema, low exercise tolerance, and FEV₁ and DLCO >20%). Despite the theoretically large number of emphysema patients globally, minimal numbers of LVRS procedures have been performed in recent years, probably due to the increased perioperative morbidity and mortality (5-20% in the first 90 postoperative days), high financial cost and technical difficulties, leading to distrust on the part of both patients and clinicians.
2. Bronchoscopic interventions for lung volume reduction are safe and exhibit minimal mortality and BLVR procedures demand comparatively much less infrastructure and experience than LVRS.
3. The data available on the application of IBV and EBV valves, but also for alveolar filling methods (BioLVR and Aeriseal) document substantial improvement in all QoL parameters as assessed by SGRQ. Bronchoscopic intervention with a low complication rate that can of-

TABLE 1. Response of patients with emphysema to bronchoscopic lung volume reduction treatment with Aeriseal

	Percentage of patients with GOLD stage III, who responded (n=14)	P	Percentage of patients with GOLD stage IV, who responded (n=11)	p
Δ FEV ₁	50%	0.048	50%	0.611
Δ FVC	64%	0.010	50%	0.736
Δ MRC	71%	0.013	13%	0.363
Δ 6MWT	36%	0.106	43%	0.288
Δ SGRQ	67%	0.048	38%	0.048

fer significant relief from difficult-to-treat symptoms, such as dyspnoea for at least 12 months, is desirable even in the absence of improvement in physiological parameters, and even that can be expected in severe pulmonary emphysema.

4. Chest HRCT scan has shown a decrease of lung volume in the target areas following treatment by IBV endobronchial valves, in comparison with an increase of volume in the non-treated areas. This volume redistribution was correlated with improvement in SGRQ but not with significant change in spirometry or exercise tolerance. The experience of the bronchoscopists in choosing the precise valve placement point, and the presence of an anatomically complete interlobal fissure, which did not allow collateral ventilation, were important parameters for treatment success. The detection of areas with collateral ventilation is crucial for the use of these techniques in heterogeneous emphysema.
5. The innovative airway bypass system achieved impressive improvement in spirometry parameters and symptom control during the first month after treatment, but early closure of stents and routes leads to a medium term loss of these benefits. So far no solution to this obstacle has been found.
6. Studies on the alveolar filling method employing the first-generation type of BioLVR and the second-generation type currently used (Aeriseal®) have demonstrated significant advantages. Improvement in QoL, exercise

tolerance, spirometry parameters and dyspnoea are reported in well chosen patient populations suffering from upper lobe, heterogeneous emphysema, but also in those with homogeneous emphysema, without significant adverse reactions. Collateral ventilation was not an issue. This treatment is not effective in all patients, and with this particular method, the results of the compound administration into the alveoli are irreversible. Data on the medium- and long-term efficacy and complications of these techniques, will probably become available in 2-4 years, and further studies are needed.

7. These studies conducted in recent years and presented in this review examine a variety of different parameters (QoL, dyspnoea, 6MWT, ergospirometry, FEV₁, FVC, TLC, DLCO, distribution of pulmonary volumes on HRCT or chest perfusion scan, survival, etc.) and exact comparison of their results is impossible. Retrospective (post hoc) analyses of the results are used for establishing the subgroups which will benefit the most, in order to determine patient enrolment criteria. This kind of analysis, although useful, can not substitute the prospective studies that are needed to confirm these results in larger numbers of these subgroups and to provide sufficient evidence for proposing a specific form of treatment. A multivariate evaluation of these bronchoscopic techniques, based on commonly accepted clinical and spirometric parameters was recently proposed by B.R. Celli (Table 2). To now, none of the

TABLE 2 Categorization of the effects of bronchoscopic lung volume reduction (BLVR) in emphysema

Category	Quality of life	Chest HRCT findings	Exercise tolerance	Spirometry	Survival (BODE index)
0	-	-	-	-	-
1	+	-	-	-	-
2	+	+	+	-	-
3	+	+	+	+	-
4	+	+	+	+	+

The suggested classification of efficacy of bronchoscopic lung volume reduction methods (BLVR) depending on clinical, imaging and spirometry parameters, and survival.

Category 1: Subjective improvement as measured by quality of life questionnaires, without spirometry or imaging parameters and without randomized trials.

Category 2: Further improvement as assessed by objective parameters (changes in HRCT and/or improvement in exercise tolerance).

Category 3: Further improvement of spirometry parameters (RV, TLC, VC, IC and FEV₁).

Category 4: A combination of symptomatic and spirometric improvement along with prolongation of survival. This combination of response in BLVR simulates the results of NETT study on lung volume reduction surgery (LVRS). Because survival follow-up in similar studies is generally short-term, the BODE index is alternatively proposed as a survival index. The evaluation of these changes is meaningful only if they last for a period greater than 6 months.

(Modified from Berger et al: Lung Volume Reduction Therapies for Advanced Emphysema: An Update. Chest 2010;138:407-417).¹⁴

TABLE 3. Evaluation of bronchoscopic lung volume reduction (BLVR) methods based on documentation of the preservation of clinical effects for >6 months in published studies.

Method	Quality of life - dyspnoea	Findings on chest HRCT	Exercise tolerance	Spirometry	Survival (BODE index)	Category
Bronchial by-pass	+ [17]	NA	+ [17]	+ [17,18]	NA	3*
Zephyr valve	+ [26,27], -[28]	± [28]	+ [26, 27, 28]	+ [26, 27, 28]	NA	3+
Spiration valve	+ [20, 21, 22]	+ [20, 21, 22]	+ [21], -[22]	- [20, 21, 22]	NA	2
Bronchial coils	+ [35]	NA	+ [35]	+ [35, --]	NA	2*
Bronchoplasty via steam	+ [38, 40]	+ [40]	+ [40]	+ [40]	NA	3¶
Method of alveolar filling- Aeriseal	+ [42-46]	+ [42-46]	+ [42-46]	+ [42-46]	NA	3

* Improvement in this study [18] was not maintained for >6 months (reported in a new study not yet published).

+ Results with marginal clinical significance.

• Results mainly from oral presentations and one publication on a small number of patients, mainly targeting the safety of the method.

¶ Oral presentation, with no publication in any international journal.

BLVR methods have demonstrated enough proof of efficacy to lead to a formal therapeutic recommendation (Table 3)¹⁰.

8. Finally, the cost-benefit relationship must be carefully examined. The cost predictions for most of the BLVR techniques so far are priced at \$ 12,000-20,000 per patient. The number of patients who would need these techniques is still undetermined. Even if some methods have been approved by the European regulatory authorities for use as a pharmaceutical device (CE mark), of the lack of completed randomized trials at present precludes elimination of the placebo effect. An international meeting of experts is deemed necessary to determine the indications and contraindications for BLVR, the emphysema subtypes to be addressed, the individual techniques and the enrolment criteria of the prospective studies that should be conducted before these techniques can become integrated into everyday practice, with international guidelines. The methods of BLVR appear on initial evidence to be safe and effective. If these findings are confirmed by large randomized trials in the future, we possibly stand at the beginning of one of the most radical therapeutic advances in the history of respiratory medicine.

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