Review Article

Lung Volume Reduction Surgery for Emphysema Treatment: State-of-the-Art and Perspectives

Eugenio Pompeo[1,2]

[1] *Department of Thoracic Surgery, Policlinico Tor Vergata, V.le Oxford, 81, 00133, Rome, Italy*
[2] *Section of Medical and Surgical Lung Diseases, Department of Biomedicine and Prevention, Tor Vergata University, Via Montpellier 1, 00133 Rome, Italy*

Correspondence should be addressed to Eugenio Pompeo; pompeo@med.uniroma2.it

Lung volume reduction surgery (LVRS) has shown an improve for up to several years respiratory function, exercise capacity, and quality of life in selected patients with severe emphysema and low exercise capacity, particularly if upper-lobe predominance of disease is radiologically recognized. However, mortality and morbidity rates of LVRS have been not negligible leading to raising question as to the cost-effectiveness of the procedure and resulting in a progressive decline in its use although a considerable number of patients meet selection criteria and could potentially benefit of this treatment modality. In recent years, an active investigation aimed at developing less invasive strategies that might allow us to achieve long-term results as satisfactory as those of the standard LVRS method but with fewer adverse effects has been undertaken. So far, novel options including nonresectional surgical and endoscopic LVRS methods hold promise but results from large studies with long follow-up are awaited to help define the most effective interventional treatment options for patients with severe emphysema. In this literature review an analysis of the main issues related to LVRS including selection criteria, mechanisms of action, results of currently available surgical and endoscopic methods, and some potential future perspectives is provided.

1. Introduction

Emphysema, one of the recognized chronic obstructive pulmonary disease (COPD) phenotypes, is an incurable, highly prevalent, and underdiagnosed condition, which represents the 4th cause of death in adults worldwide [1].

It is defined as an abnormal permanent enlargement of air spaces distal to the terminal bronchiole associated with destruction of their walls [2].

Pathophysiology of emphysema include reduced area for gas exchange and decreased lung elastic recoil with early expiratory airway collapse and increased airflow resistance resulting in lung hyperinflation. This effect is exaggerated during exercise when dynamic hyperinflation further impairs respiratory mechanics, increases work of breathing, and may even hinder cardiac filling, leading to dyspnea and reduced exercise performance. The cascade of detrimental effects of emphysema eventually impairs quality of life and increases mortality [3–6].

In the last 2 decades lung volume reduction surgery (LVRS) has emerged as an effective treatment modality, which can reverse detrimental effects of emphysema for a variable period of time leading to significant and long-lasting improvements in respiratory function, exercise capacity, quality of life, and survival [7–13].

Randomized studies [14–20] including the large multi-institutional National Emphysema Treatment Trial (NETT) [21] have confirmed that LVRS can offer superior benefits than optimized medical therapy including respiratory rehabilitation, particularly in patients with upper-lobe predominant emphysema and low exercise capacity. However, provided the fragile clinical status of patients with advanced emphysema, mortality and morbidity rates of LVRS have been not negligible and in the NETT up to 28% of patients

have been reported to need in-hospital stay or rehabilitation facilities for 1 month or more after surgery [22].

These figures have led to raising question about the cost-effectiveness of LVRS [23] and have stimulated the development of potentially less morbid strategies of treatment.

Thus fur, quite many LVRS-related issues still merit further investigation and a number of novel surgical [12, 20] and bronchoscopic lung volume reduction (BLVR) methods are under active scrutiny [24–37].

In this review I sought to critically analyze the current state-of-the-art and potential future perspectives on this topic.

2. Background

LVRS was proposed in 1957 by Brantigan and Mueller [38] who performed bilateral nonanatomic resection of emphysematous lung tissue through staged thoracotomy. They believed that a reduction of 20–30% of the overall lung volume would have led to a more physiologic reconfiguration of the chest wall and diaphragm as well as restoring radial traction on the bronchi, thereby relieving expiratory flow obstruction [39].

By 1961, Brantigan et al. [40] had performed LVRS on 56 patients. Unfortunately although nearly 90% of the patients had improved in symptoms, LVRS was rapidly abandoned at that time because of an 18% mortality rate and the lack of objectively documented benefits.

About 4 decades later, Cooper et al. [7] revisited Brantigan's idea proposing some technical refinements to the original procedure including use of median sternotomy and simultaneous (one-stage) bilateral staple lung resection. In that study there was no operative mortality and comprehensive outcome assessment showed significant improvements in dyspnea, pulmonary function, exercise tolerance, quality of life measures, and rate of independency from supplemental oxygen. Thereafter, several other surgical teams produced similar satisfactory results and in an attempt to reduce the typical procedure-related morbidity reported with open approaches, LVRS started being performed also by video-assisted thoracic surgery (VATS) either unilaterally [41–43] or bilaterally [44–47].

3. Selection Criteria

LVRS can be considered in patients, with COPD who are severely symptomatic and fail to improve despite optimized medical treatment including pulmonary rehabilitation.

Patients in whom predominant emphysema is suspected to be following medical history, routine chest roentgenograms and spirometry, should undergo high-resolution computed tomography (CT), measurement of static lung volumes by body plethysmography, and assessment of diffusing capacity for carbon monoxide (DLCO).

A diagnosis of severe emphysema with disabling dyspnea, moderate-to-severe obstructive defect, high residual volume (RV), and limited exercise capacity are amongst standard inclusion criteria [48] (Table 1).

TABLE 1: Suggested main selection criteria for LVRS.

Inclusion criteria	Exclusion criteria
Age ≤ 80 years	BMI < 18 > 29
Severe, heterogeneous emphysema, preferably predominant in the upper lobes at the HRCT.	Severe, homogeneous emphysema with no target areas for LVRS at the HRCT.
Dyspnea at rest or with minimal physical activity (MMRC score ≥ 3).	Need of ventilatory assistance.
Moderate to severe obstructive defect with $FEV_1 \leq 45\%$ but > 20% predicted.	DLCO < 20% predicted by the single breath technique.
Functional aspects of hyperinflation with residual volume >180% predicted and total lung capacity >120% predicted on body plethysmography.	Significant bronchitis with increased inspiratory airway resistance and/or abundant daily sputum production.
Resting room PaO_2 > 45 mmHg	Resting $PaCO_2$ > 55 mmHg
Impaired exercise capacity but 6MWT distance > 140 m.	Pulmonary hypertension with mean PA pressure >35 mmHg or peak systolic PA pressure >50 mmHg on Doppler echocardiography.
ASA score ≤ 3.	Any comorbid condition that would significantly increase operative risk.
Quit smoking for at least 4 months.	Neoplastic disease with life expectancy < 12 months.

HRCT: high-resolution computed tomography; LVRS: lung volume reduction surgery; MMRC: modified Medical Research Council dyspnea score; FEV_1: forced expiratory volume in one second; DLCO: diffusion capacity for carbon monoxide; PaO_2: arterial oxygen pressure; $PaCO_2$: arterial carbon dioxide pressure; 6MWT: 6-minute walking test; PA: pulmonary artery; ASA: American Society of Anesthesiology score.

Radiologically, candidates for LVRS should disclose signs of lung hyperinflation with flat diaphragms on chest X-rays and areas of severe emphysema intermingled with better preserved lung tissue (heterogeneous emphysema) on CT scan (Figure 1).

The NETT definitively confirmed previous studies' findings indicating that patients, with upper-lobe predominant emphysema and low exercise capacity represent the ideal candidates for LVRS in terms of expected magnitude and duration of benefits [21].

NETT also indicated that patients with forced expiratory volume in one second (FEV_1) ≤ 20% predicted and either homogeneous emphysema or DLCO ≤ 20% predicted, had a mortality rate of 16% and should thus be considered noneligible for the operation [49].

An asymmetric distribution of emphysema with more severe destruction in a single lung has been considered as an elective indication for unilateral LVRS [11, 42].

Inspiratory resistance of the airways, though not commonly employed, has been proposed as a marker of the
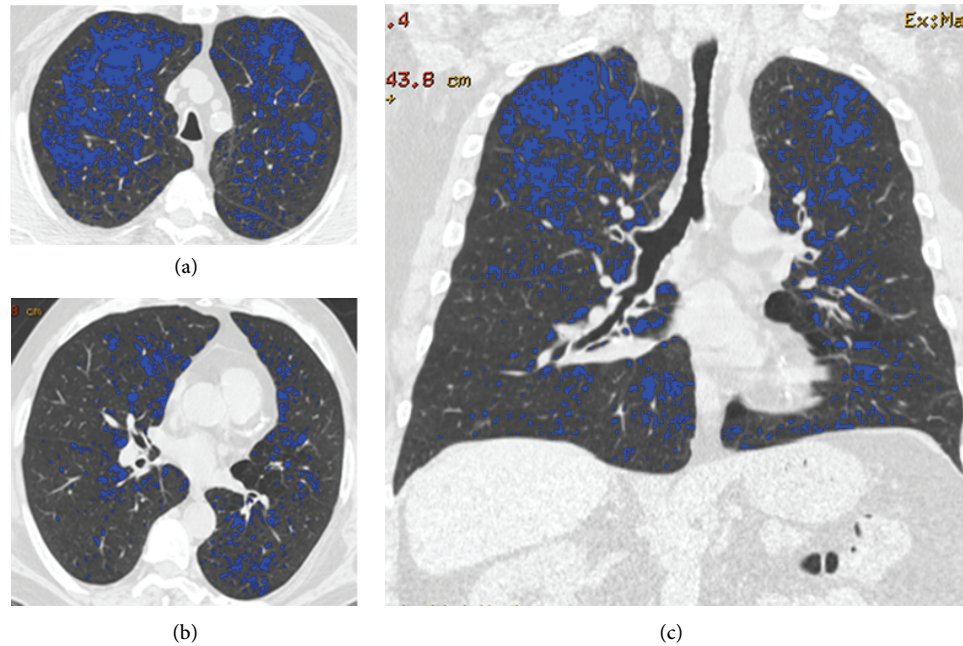
(a)

(b)

(c)

FIGURE 1: Axial ((a) and (b)) and coronal (c) TC imaging of an optimal candidate for LVRS due to severe upper-lobe predominant emphysema associated with relatively better preserved lower lobes lung tissue. Multiplanar reconstruction algorithm allows quantifying the extent of emphysema and provides coloured contrast enhancement (in blue) of the target regions for LVRS.

bronchitis component, with high values deemed to predict a poor response to LVRS [50]. However, Washko and coworkers [51] reported that static lun recoil pressure at total lung capacity (TLC), inspiratory resistance, and CT measures of the airway disease did not predict improvements in either FEV1 or maximal exercise.

Hypoxemia and need of supplemental oxygen are commonly found in LVRS candidates and usually do not contraindicate the procedure.

Stable abstinence from cigarette smoking is mandatory to minimize operative risks and confirm the patient's motivation to be enrolled in a surgical program.

If it does exist the suspicion of latent or occult ischemic cardiac disease, a careful investigation including pharmacologic stress test and, if necessary, coronary angiography, should be performed due to the high prevalence of coronary artery disease in patients with COPD [52].

Exclusion criteria include lack of adequate heterogeneity on CT imaging and too severely impaired respiratory function or exercise capacity, as well as comorbid conditions that are likely to predict a poor response to LVRS or to increase prohibitively the surgical risk (Table 1).

4. Mechanisms of Improvement

Surgical removal of hyperinflated and emphysematous lung tissue induces mechanical stretching of the remaining lung. An unchanged chest wall operating on a smaller lung is thought to partially restore the elastic recoil [53] whereas the expiratory flow at any given lung volume is thought to increase due to improved airway traction and delayed airway closure. Reduced thoracic gas compression and improved expiratory flow may translate into improvement in chest wall and diaphragm configuration/mechanics, reduced dynamic hyperinflation [54] and work of breathing, and better cardiac performance [55].

4.1. Lung Elastic Recoil. Sciurba and coworkers [56] first reported that lung elastic recoil can improve after LVRS and that the greater is the increase in elastic recoil, the greater the maximal improvements in exercise tolerance, and the larger the decrease in RV. In addition, Gelb and coworkers [57] have found a correlation between improvements in elastic recoil and decreased transmural pressure, improved airway conductance, and better expiratory airflow. However, Ingenito and coworkers [58] reported that improvement in expiratory flows after LVRS can be largely accounted for by increases in vital capacity without significant changes in the FEV_1 to forced vital capacity (FVC) ratio. These findings support the theoretical model proposed by Fessler and Permutt [59], according to which, following LVRS, the increase in FVC is the result of a resizing of the lung to the chest wall, which in turn induces an increase in recoil pressure at any given lung volume, without producing changes in either small airway conductance, airway closing pressure, or compliance. On the other hand, Tschernko and coworkers [60] found that measures reflecting the efficiency of ventilatory mechanics including work of breathing, intrinsic positive end-expiratory pressure, and dynamic compliance, improved all after LVRS due to a relief of thoracic distention and reduced airway resistance.

4.2. Chest Wall and Diaphragm Configuration. Lando and coworkers [61] reported that LVRS decreases middle-to-lower anterior-to-posterior rib cage diameter as assessed by chest radiography and CT whereas, in another elegant study, Cassart et al. [62] have found that by decreasing the overall lung volume, LVRS makes the diaphragm dome move upwards and increases the area of muscle juxtaposed to the rib cage. Lower operating lung volumes have been reported to eventually lead to improvements in strength and efficiency of inspiratory muscles.

Bloch and coworkers [63], by employing respiratory inductive plethysmography, had shown that during quite breathing, LVRS did not increase tidal volume, respiratory cycle times, or minute ventilation but resulted in better synchronization of rib cage-abdominal motion due to greater contribution of abdominal volume changes to tidal volumes, which were deemed consistent with lower inspiratory loading and greater force-generating capacity of the diaphragm.

4.3. Gas Exchange. Beneficial effects of LVRS on gas exchange have been attributed to an improved regional ventilation or perfusion matching that follow the recruitment of previously compressed but functionally preserved lung regions [64] although results of LVRS on arterial oxygenation have been variable. Some investigators [65, 66] have found that LVRS can increase arterial oxygen tension (PaO_2 in a significant manner whereas Geddes et al. [15] reported trivial improvement of PaO_2 and arterial carbon dioxide tension ($PaCO_2$) after surgery. However, a recent meta-analysis of randomized trials indicated that following LVRS, significant improvements occur both in PaO_2 and $PaCO_2$ [67]. In an analysis of the NETT cohort, Criner and coworkers [68] reported that following LVRS, patients with upper-lobe emphysema on maximal exercise showed higher output of CO_2, greater tidal volume, and increased hearth rate, which were associated with slower and deeper breathing patterns lasting for up to 24 months.

4.4. Oxygen Consumption. Takayama and coworkers [69] reported a significant reduction in oxygen cost which proved inversely correlated with improvements in FEV_1 ($R = -0.70$, $P < 0.001$) and directly correlated with RV/TLC ($R = 0.54$, $P < 0.01$). In addition LVRS reduced oxygen consumption of respiratory muscles at maximal ventilation from 55.5% to 49.0% ($P < 0.05$).

Our group [70] reported that LVRS significantly decreased oxygen consumption volume and resting energy expenditure when compared to the effects of respiratory rehabilitation and that substrate oxidation changed from prevalent lipid to prevalent carbohydrate. The significant correlations we have found with RV and nutritional status suggested improvements in respiratory mechanics, energy expenditure and metabolism towards normal ranges.

4.5. Cardiocirculatory Function. Right and left ventricular function can be impaired in patients with advanced emphysema due to reduced end-diastolic volumes. On the other hand beneficial effects of LVRS on right ventricular filling and

performance have been hypothesized by our group [71] who reported that improvements in right ventricular function indexes occurred on exercise after LVRS and correlated with a reduction in RV/TLC. In a similar manner, Jörgensen et al. [72] reported post-LVRS increases in left ventricular end-diastolic dimensions and filling, eventually resulting in improved left ventricular function.

In an analysis from the NETT on pulmonary hemodynamic changes at rest, Criner et al. [73] reported that except for a smaller change in end-expiratory capillary wedge pressure, compared with medical treatment, LVRS was not associated with an increase in pulmonary artery pressures. On the other hand, due to the typically irregular distribution of emphysema, removal of lung areas receiving substantive degrees of perfusion must be limited at most since a reduction in pulmonary vascular bed due to LVRS, anecdotally resulted in pulmonary hypertension [74].

5. One-Stage Bilateral LVRS

One-stage bilateral LVRS is the most widely adopted approach since it produced greater functional and clinical improvements than unilateral treatment [43, 75].

The standard technique entails nonanatomical staple resection of the most emphysematous lung tissue (resectional LVRS) carried out on both lungs by median sternotomy [9, 10] or VATS [44, 46] through general anesthesia and single-lung ventilation.

Results of bilateral LVRS proved comparable either by VATS or median sternotomy [76] although satisfactory results have been also achieved through bilateral staged thoracotomy [77] or the clamshell incision [78].

VATS has been deemed more difficult to be accomplished in presence of pleural adhesions although feasibility by this approach has been shown to be usually not compromised by pleural adhesions [79].

5.1. Mortality and Morbidity. The poor clinical status of patients undergoing LVRS has resulted in mortality and morbidity rates that have been not negligible. In fact, mortality rates ranged between 0 and 17% in previous studies (Table 2) whereas an overall morbidity rate of 59% has been reported in the NETT [22]. In this large study, major pulmonary and cardiovascular morbidity within 90 days post-LVRS occurred in 30% and 20% of patients, respectively. Cardiac arrhythmia was the most common complication with a rate of 23.5%. Rates for pneumonia and need of reintubation were 18% and 22%, respectively. Other reported causes of morbidity include bleeding, respiratory failure and gastrointestinal complications whereas late complications after LVRS include pulmonary hypertension [74], secondary pneumothorax [80], metallophtysis (i.e., asymptomatic expectoration of steel staples) [81], and the development of giant bullous emphysema [82].

In a further analysis from the NETT comparing median sternotomy versus VATS results [76], 90-day mortality was 5.9% for median sternotomy and 4.6% for VATS with no intergroup difference. Hospital stay was also comparable but

TABLE 2: Perioperative results of randomized studies on LVRS.

First author	Year	Total/ surgical arm (N)	Surgical approach	LVRS method	LVRS extension	Operative mortality (%)	Morbidity (%)	Hospital stay (mean)
Criner [14]	1999	37/32	MS	Resectional	Bilateral	9.4	15.6[M]	—
Geddes [15]	2000	48/23	MS/VATS	Resectional	Bilateral	17	22[A]	19
Pompeo [16]	2000	60/30	VATS	Resectional	Unilateral/bilateral	3.3	53[A]	13.6
Goldstein [17]	2003	55/28	VATS/MS	Resectional	Bilateral/unilateral	7.1	14.2[M]	—
DeCamp Jr [22]	2008	1218/608	MS/VATS	Resectional	Bilateral	5.2	58.7[A]	—
Hillerdal [18]	2005	105/49	MS/VATS	Resectional	Bilateral	12	—	—
Miller [19]	2006	93/54	MS/VATS	Resectional	Bilateral	1.5	—	12–22
Pompeo [20]	2012	63/31[*]	VATS	Resectional	Unilateral	3.2	48.3[A]	7.5°
		63/32[*]	AVATS	Nonresectional	Unilateral	0	18.7[A]	6°

LVRS: lung volume reduction; MS: median sternotomy; MS: median sternotomy; VATS: video-assisted thoracic surgery; AVATS: awake VATS; [*]both arms were surgical. [A]All events; [M]major morbidity; °median value.

30 days after surgery patients who were living independently were 70.5 % after median sternotomy compared to 81% after VATS ($P = 0.02$). In addition, overall costs related to LVRS were less for VATS compared to median sternotomy ($P = 0.03$).

Naunheim and colleagues [83] analyzed risk factors for mortality and morbidity amongst NETT nonhigh risk patients. They have found that age, FEV_1, and DLCO were risk factors for major pulmonary morbidity whereas non-upper-lobe predominant distribution of emphysema increased operative mortality and cardiovascular morbidity with odds ratios of 2.99 and 2.67, respectively. Conversely, in contrast to previous literature, NETT data did not indicate hypercapnia or poor exercise tolerance as predictors of worse outcome although a potential bias in the NETT was the intentional exclusion of patients with a $PaCO_2 > 60$ mmHg (55 mmHg in one Center) and of those walking 140 m or less on 6-minute walking test (6MWT) [52].

Air leaks represent the most frequent minor adverse event after LVRS occurring in up to 90% of patients postoperatively and lasting more than 30 days in about 12% of instances [84].

To limit the occurrence of air leaks, use of exogenous buttressing material along the suture lines of lung tissue resection was recommended [85–89].

Cooper and coworkers [85] reported prolonged air leaks in 46% out of 150 patients undergoing bilateral LVRS with bovine pericardium buttress and pleural tenting used as adjunctive sealant methods.

Hazelrigg et al. [90] reported on a slight reduction of air leaks duration and hospital stay with buttressed LVRS with no cost advantage. Moreover, in a three-centre randomized study comparing bovine pericardium buttress versus no buttress [91], a significant reduction in air leaks was found in the buttressed group whereas no difference was detected in hospital stay amongst study groups.

DeCamp et al. [84], in a post hoc analysis of the NETT, have found no advantage in air leaks duration with the use of various buttressing material including bovine pericardium, polytetrafluoroethylene, or fibrin glue. Air leaks duration was longer in caucasians and in association with lower FEV_1 or DLCO, use of inhaled steroids, upper-lobe predominant emphysema, and presence of pleural adhesions. Postoperative complications were greater in patients with air leaks (57% versus 30%, $P = 0.0004$) and postoperative stay was longer (11.8 ± 6.5 days versus 7.6 ± 4.4 days, $P = 0.0005$).

Finally, in a more recent comparative analysis of resectional versus nonresectional LVRS, we have found that at univariate analysis, resectional LVRS, higher severity of emphysema and lower DLCO correlated significantly with occurrence of prolonged air leaks, whereas at multivariate analysis, higher severity of emphysema was the only factor predicting prolonged air leaks (odds ratio = 4.85, $P < 0.0001$) [92].

5.2. Clinical Outcome. Reported benefits of LVRS include significant improvements in respiratory function, exercise capacity [7–14], subjective dyspnea [93], quality of life measures [94–96], and survival [99]. Other less frequently reported benefits include improvements in oxygenation [64–67], body weight, and nutritional status [97, 98], cardiac function [71, 72], cognitive function [100], alveolar ventilation [101], and breathing pattern [63, 68].

In particular, Ciccone et al. [9] reported that FEV_1 improved at 6 months by up to 56% whereas RV, 6MWT, and short-form-36 physical functioning quality of life domain (SF-36 PF) improved acutely by 33%, 25%, and 67%, respectively, and remained significantly improved for up to 5 years. In addition, in a series from Gelb et al. [8], FEV_1 improved by more than 200 mL and/or FVC by more than 400 mL for up to 4 and 5 years, in 27% and 8%, of 26 patients with complete follow-up data, respectively. Overall, superior and longer lasting benefits have been reported in patients with upper-lobe predominant emphysema [9, 21, 48]. However, Weder and coworkers [13] reported satisfactory improvements for up to 36 months even in patients with homogeneous emphysema who also showed a 5-year survival

comparing that of patients with heterogeneous disease (64% versus 73%).

In the NETT [21], 1218 patients were randomized to receive either LVRS or medical therapy. Maximal exercise capacity improved ≥10 W in 28%, 22%, and 15 % of 608 LVRS patients after 6, 12, and 24 months, respectively, compared to 4%, 5%, and 3% of control group patients. Additionally, patients who underwent LVRS were more likely to achieve improvements in 6MWT, FEV_1, severity of dyspnea, and quality of life measures compared to the control group.

One important feature of the NETT was that overall results were analyzed also according to some baseline characteristics including the craniocaudal distribution of emphysema on chest CT and results of postrehabilitation maximum exercise capacity. The combinations of high and low exercise capacity with upper-lobe or non-upper lobe predominance of emphysema at the chest CT led to division of patients into 4 subgroups.

At a mean follow-up of 2.4 years, in 290 patients with upper-lobe predominant emphysema and low exercise capacity, LVRS resulted in a lower risk of death than medical therapy (RR 0.47, $P = 0.005$). Also, this subgroup more likely achieved a meaningful improvement in maximum exercise (≥10 W) at 24 months (30% versus 0%; $P < 0.001$) and an improvement in quality of life defined by a reduction of the St. George's Respiratory Questionnaire (SGRQ) ≥ 10 points (48% versus 10%; $P < 0.001$).

Amongst 419 patients with upper-lobe predominant emphysema and high exercise capacity, LVRS had no impact on survival but was more likely to induce an improvement in maximum exercise testing at 24 months (15% versus 3%, $P = 0.001$ and SGRQ (41% versus 11%, $P < 0.001$) as compared to medical therapy.

In 149 patients with non-upper-lobe predominant disease and low exercise capacity, LVRS had no impact on survival or maximum exercise capacity. However, surgery was more likely to improve SGRQ at 24 months (37% versus 7%, $P = 0.001$).

Finally amongst 220 patients with non-upper-lobe predominant emphysema and high exercise at baseline, LVRS increased the risk for death (RR 2.06, $P = 0.02$) and had no effect on maximum exercise capacity or quality of life at 24 months.

Recently, Lammi and coworkers [102], in a 59-patients series of patients undergoing LVRS with the same selection criteria employed in the NETT, reported a higher rate of responders in 6MWT (increase >54 m) at 6 (46% versus 28%) and 12 months (51% versus 28%) and in FEV_1 (increase >12% or 200 mL) for up to 36 months (57% versus 29%).

As far as less commonly reported beneficial effects of LVRS are concerned; Washko and coworkers [103] have shown in an ancillary NETT study that surgery reduced by about 30% the rate of COPD exacerbation, an effect which did not occur in the medical arm and which correlated with the degree of improvement in FEV_1. In another ancillary NETT analysis, Kozora and coworkers [100] reported that 6 months after LVRS patients improved in psychomotor speed, verbal memory, and naming skills. In addition, surgical patients had a greater decline in depressive symptoms compared

with patients in the medical arm. Finally, Armstrong et al. [104] investigated response to LVRS versus medical therapy of chronotropic incompetence, which is a marker of poor prognosis in patients with COPD. They found that 6 months after LVRS, mean percent of predicted heart rate reserve improved from 41% to 50% ($P < 0.001$) whereas no change occurred in the control group.

A longer-term follow-up analysis of the NETT [10] with a median follow-up of 4.3 years has shown that despite an expected higher postoperative mortality, LVRS offered a survival advantage compared to medical treatment (total mortality, 0.11 deaths per person-year with LVRS and 0.13 with medical therapy, $P = 0.02$).

At follow-up of 1, 2, and 3 years, exercise capacity improved 10 W or more in 23%, 15%, and 9% of LVRS patients, respectively, compared with 5%, 3%, and 1% of the medical patients ($P < 0.001$ at each time point). In addition, after LVRS, SGRQ score improved (decreased) by 8 units or more in 40%, 32%, 20%, 10%, and 13% compared to 9%, 8%, 8%, 4%, and 7% following medical care at 1–5 years of follow-up (years 1–3, $P < 0.001$; year 4, $P = 0.005$; year 5, $P = 0.12$). Furthermore, in 290 patients with upper-lobe predominant emphysema and low exercise capacity, LVRS provided a substantial survival advantage compared to medical treatment and also greater improvements in exercise capacity and quality of life.

In a further analysis, Chandra et al. [105] suggested a complimentary role of lung perfusion scintigraphy with high-resolution CT and identified as optimal responders to LVRS patients with both upper-lobe predominant emphysema at CT scan and low upper-lobe perfusion (<20% of the total) at perfusion scintigraphy.

6. Unilateral LVRS

Theoretically, unilateral LVRS could offer the advantage to be a less morbid surgical approach than one-stage bilateral treatment, particularly if VATS is the preferred approach [76, 106, 107]. Unfortunately so far, no randomized study has compared results of unilateral versus bilateral LVRS and the former has been mainly employed as a second choice option in patients with previous thoracic surgery or pleurodesis on one, side and in those who were deemed unfit for a bilateral procedure due to advanced age or associated comorbidities [108].

As expectable, bilateral LVRS produced greater improvement in FEV_1, dyspnea, and exercise capacity than unilateral procedures [109]. However, Brenner et al. [107] have reported that FEV_1 improved 39% following a bilateral and 25% after unilateral LVRS, a finding which suggests the potential of unilateral LVRS to affect the function in the nonoperated lung due to lungs-compliance-related interdependence [110]. Moreover, in the study from Brenner et al. [107] FEV_1 decay averaged 255 mL/year after bilateral LVRS and 107 mL/year after unilateral procedures, leading to hypothesize that simultaneous bilateral treatment induces a greater mechanical stress in the lungs, which may translate in a steeper functional decay than after unilateral LVRS.

TABLE 3: Operative results of unilateral LVRS.

First author	Year	Surgical approach	Patients (N)	Mortality (%)	Hospital stay	FEV$_1$ increase (%)
Keenan [41]	1996	VATS	67	5.9	17	27
McKenna Jr [109]	1996	VATS	87	3.5	11.4	31
Keller [93]	1997	VATS	25	0	8.8	31
Argenziano [78]	1997	MS/VATS	28	3.6	—	28
Kotloff [43]	1998	MS/VATS	32	0	14.2	24
Geiser [152]	2001	VATS	28	0	—	18
Mineo [11]	2005	VATS	97	1.03	9*	36
Meyers [153]	2008	T/MS	43	2.3	8*	25

FEV$_1$: forced expiratory volume in one second; MS: median sternotomy; VATS: video-assisted thoracic surgery; T: thoracotomy; *median value.

In other reported series, unilateral LVRS resulted in mortality rates of 0–2.3%, a hospital stay of 8–17 days, and a % increase of FEV$_1$ of 18–31% (Table 3).

Surgically oriented visual grading systems [111] and quantitative CT analysis [110] have been developed to help identify optimal candidates for unilateral treatment. In fact, by applying a visual grading system we have found that FEV$_1$ improved up to 500 mL in patients with heterogeneous but symmetric emphysema undergoing one-stage bilateral LVRS, and 440 mL in patients with asymmetric emphysema undergoing unilateral treatment [111].

In a multi-institutional comparative study, Lowdermilk and colleagues [112] reported that FEV$_1$, FVC, RV, quality of life, and dyspnea improved significantly more after bilateral than after unilateral LVRS whereas no intergroup difference was found in arterial oxygenation, 6MWT, and decrease in oxygen utilization.

In a series of 97 patiens undergoing intentional unilateral LVRS by VATS, we reported that following significant peak improvements at 6 months, FEV$_1$, RV, 6MWT, and SF-36 PF domain score were still improved by 24%, 18% and 100% at 3 years. In addition, RV, 6MWT, and SF-36 PF remained significantly better than baseline values for up to 5 years [11].

In a retrospective study, Serna and coworkers [113] reported 2-year survival of 86% and 73% after bilateral or unilateral LVRS, respectively. In addition, in a multi-institutional study [114] 3-year survival was 69% after unilateral and 74% after bilateral LVRS with no intergroup difference.

7. Staged Bilateral LVRS

The steeper postoperative decay in FEV$_1$ observed with bilateral LVRS [107] and the possibility that unilateral treatment could positively affect the function of both lungs support a role for staged treatment. Nonetheless, data regarding the results of staged bilateral LVRS is scarce and so far no randomized comparisons with one-stage bilateral treatment do exist.

Kotloff et al. [43] reported that following staged bilateral LVRS, the contribution of each procedure to the peak improvement in FEV$_1$ was 0.14 L after the first procedure and 0.13 after the second. Hazelrigg et al. [47] analyzed the results of one-stage versus staged bilateral LVRS. In the staged group by adopting a standardized 3 to 4 months interval between

the procedures, complication rate and early outcomes were comparable but the sum of 2 hospitalizations times was longer than that in the one-stage group. Conversely, our group [115] reported on a comparative analysis of staged versus one-stage bilateral LVRS in which the completion of the bilateral treatment was performed at the reappearance of severe disability. The mean interval between staged procedures was 15.2 months and although peak improvements were greater in the one-stage group, improvements in FEV$_1$, FVC, RV, and 6MWT distance were more stable in the staged group. In addition at 36 months, RV was significantly lower in the staged group (4.6 L versus 5.3 L, $P = 0.01$).

In a further report we have shown that amongst 97 patients undergoing intentional unilateral LVRS, 70% were still free from contralateral treatment at 5 years. Such a finding suggests that in selected patients postponement or even definitive avoidance of the contralateral treatment can be achieved by a staged strategy of treatment [11].

In accordance with our findings, Oey and coworkers [106] analyzed results of a 114-patients cohort undergoing one-stage bilateral (26 patients) or unilateral (88 patients) LVRS that included the possibility of a staged bilateral procedure performed on patients request. At a median follow-up of 2.8 years, a staged bilateral treatment was performed in 16 patients with a median interval between the procedures of 3.9 years. There was no difference between the 3 groups in operative mortality and 5-year survival. However, results in the domain of physical functioning, social functioning, and energy/vitality were still significantly improved at 4 and 6 years, respectively, in the staged group only.

8. LVRS and Lung Transplantation

Lung transplantation and LVRS have both demonstrated to improve dyspnea, respiratory function, exercise capacity, and quality of life in patients with severe emphysema. However, due to a partial overlapping of selection criteria, identification of the appropriate candidate for each option is mandatory [116].

The age limit for lung transplantation is commonly 60–65 years. For older patients, LVRS remains the only surgical option to achieve a significant clinical benefit whereas patients aged 55–60 are more difficult to address since the

benefits of LVRS may be lost over time when they reach an age limit which may be critical for lung transplantation.

In young patients who fulfill the criteria for both surgical treatments, LVRS can be performed first to postpone lung transplantation and thus avoid the negative side effects of chronic immunosuppression and medication. This is especially the case when heterogeneous distribution of emphysema is recognized on CT and perfusion scans because LVRS proved to be able to delay the need for lung transplantation by 3–6 years [117, 118]. Conversely, findings of homogeneous or α-1-antitrypsin-deficiency-related emphysema, a $FEV_1 <$ 20% predicted, a DLCO < 20% predicted, and an elevated pulmonary artery pressure as well as the presence of scarring of the lungs or chronic inflammatory changes are also preferably addressed to lung transplantation [49, 116, 119].

LVRS and lung transplantation may be complimentarily combined in several ways.

LVRS has been employed as a bridge to transplantation [120, 121] simultaneously with single lung transplantation to prevent native lung hyperexpansion [122] and early or late posttransplant to treat native lung hyperexpansion [123, 124].

As a rule, lung transplantation can be performed safely after LVRS with no adjunctive adverse effects although a higher number of blood transfusions may be required due to adhesions being developed after initial LVRS [117, 122], particularly if buttressed stapling devices have been employed. Nathan et al. [125], in a comparative analysis including 50 patients undergoing LVRS followed by lung transplant, and 741 patients undergoing sole lung-transplant, reported no intergroup difference in the need for reoperation, hospital stay, or survival. More recently, Shigemura et al. [126] reported that out of 177 lung transplant patients, a higher incidence of postoperative bleeding requiring reexploration and of renal dysfunction requiring dialysis occurred in 25 patients who underwent LVRS before lung transplantation. In addition in this series, peak FEV_1 improvement was worse in patients with LVRS before lung transplantation (56.7% versus 78.8%; $P < 0.05$) whereas 5-year survival was similar between the groups (59.7% versus 66.2%).

9. Nonresectional LVRS

Historical background of nonresectional LVRS includes the technique developed by Crosa-Dorado et al. [127] in 1992, who proposed multiple fold plication of the most emphysematous regions performed by thoracotomy under general anesthesia. The technique was subsequently adapted by Swanson et al. [128] for a more reliable VATS application. A slightly different fold plication method was proposed subsequently by Iwasaki and coworkers [129].

In 2006, our group [130] reported feasibility and early results of a novel nonresectional LVRS technique, which entails an introflexive plication of the most emphysematous lung regions and was developed to be ideally performed in spontaneously ventilating awake patients through thoracic epidural anesthesia. This original method respects the basic concepts of resectional LVRS including a reduction of about 30% of the overall lung volume, suturing performed along

a single ideal line and use of stapling devices. Yet, it adds some potential advantages including peripheral suturing, a linear but interrupted suture line which is more flexible, avoidance of any pleural discontinuation, and a 4-fold inlay buttress created by the plicated bullous tissue itself, which are aimed at facilitating postoperative lung reexpansion and at reducing the occurrence of air leaks.

Subsequently, in a 42-patients series we reported no 90-day mortality with significant 2-year improvements in 6MWT, FEV_1, FVC, and RV, and in the multidimensional body mass index, airflow obstruction, dyspnea, and exercise capacity index (BODE) [12].

More recently, our group [20] published results of a randomized study entailing 63 patients receiving awake nonresectional LVRS (32 patients) or standard resectional LVRS through general anesthesia (31 patients). In this study the proportion of patients who could be discharged within 6 days was significantly greater in the awake group (21 versus 10 patients, $P = 0.01$). Nonfatal adverse events including air leaks were significantly less in the awake group (7 versus 16, $P = 0.01$). At 6 months, FEV_1 improved significantly in both study groups (0.28 L versus 0.29 L, $P = 0.81$) as did FVC, RV, 6MWT, and SF-36 PF score, which remained significantly better than baseline values for up to 24 months. At 36 months, freedom from contralateral treatment (55% versus 50%, $P = 0.7$) and survival (81% versus 87%, $P = 0.5$) were comparable. A comparison of clinical results between nonresectional and resectional LVRS is depicted in Table 4.

10. Redo LVRS

A poorly investigated issue regards LVRS performed a second time on the same thoracic cavity (redo LVRS). It may be indicated in strictly selected patients who already underwent successful bilateral LVRS but have lost the initial benefit and have developed further lung target areas amenable to be excised or plicated surgically.

Stammberger et al. [131] first reported on a patient with alpha-1-antitrypsin deficiency emphysema who underwent redo LVRS with satisfactory outcome.

More recently our group [132] analyzed the results of a 17 patients series on redo LVRS. In this series, the surgical procedures entailed completion lobectomy in 7 patients and nonanatomic lung resection under general anesthesia or awake lung plication under epidural anesthesia in 5 patients each. Operative mortality was 11.7% (2 patients). The mean hospital stay was 9 days. Significant improvements occurred for up to 12 months in FEV_1 ($P < 0.001$), FVC ($P < 0.002$), RV ($P < 0.001$), 6MWT ($P < 0.001$), and dyspnea index ($P < 0.001$). In particular, at 6 months, improvements in FEV_1 were greater than 200 mL in 11 patients and correlated with the postoperative reduction in RV ($R = 0.62$, $P = 0.01$).

11. Bronchoscopic Lung Volume Reduction

The typical LVRS-related morbidity has contributed to stimulate the development of investigational bronchoscopic lung volume reduction (BLVR) methods, which are currently

TABLE 4: Results of randomized studies on LVRS*.

First author	Year	Time of assessment (months)	FEV$_1$	RV	6MWT	PaO$_2$	DLCO	Quality of life
Criner [14]	1999	3	31	−24.5	9.4	—	16.6	—
Geddes [15]	2000	6	23	−28	29	−4.1	—	41 (SF-36)
Pompeo [16]	2000	6	53	−25	24	7	—	—
Goldstein [17]	2003	6	37.5	−16	4.1	—	—	—
Hillerdal [18]	2005	6	24	−25	35	5.2	—	32 (SGRQ) 111 (SF-36, PF)
Miller [19]	2006	6	27.5	−25	13	—	15	—
Pompeo [20]	2012	6	36	−17.4	27	4.4	—	75.8 (SF-36, PF)
			35§	−20.8§	31§	5.8§	—	110 (SF-36, PF)§

*Surgical arms results of studies in which % change from baseline values was computable are included. LVRS: lung volume reduction surgery; FEV$_1$: forced expiratory volume in one second; RV: residual volume; 6MWT: 6-minute walking test; PaO$_2$: arterial oxygen pressure; DLCO: diffusion capacity for carbon monoxide; SF-36: short form 36-items questionnaire; SGRQ: St.George questionnaire; PF: physical functioning domain score. §Results of awake nonresectional LVRS.

actively investigated. The main approaches can be divided into use of bronchial blocking devices, of devices working at the lung tissue level, and creation of extra-anatomical airways [133].

11.1. Bronchial Blocking Devices

11.1.1. Plugs. These devices are aimed at occluding the target bronchus leading to atelectasis and lung volume reduction.

So far, the only available plugs are the "Watanabe spigots" which are made of silicon and have a truncated conical shape with lateral studs to facilitate bronchial anchorage [134]. Watanabe spigots were initially introduced to treat pulmonary fistula and persistent pneumothorax with prolonged air leakage but have also been used to achieve BLVR in emphysema.

Results are limited to a small clinical series in which some clinical improvements and a 12.5% rate of pneumonias did occur [135]. A multicenter study using Watanabe spigots to treat emphysema is ongoing in Japan.

11.1.2. Endobronchial Valves. One-way endobronchial valves implanted into the airway are the most widely studied devices for BLVR. Their mechanism of action is promoting atelectasis of the target lung region/lobe by blocking regional inspiration but permitting expiration and drainage of secretions.

Currently, two types of valves have been more widely investigated: Zephyr valves (Pulmonx, Inc., Palo Alto, CA, USA) and IBV valves (Spiration Inc., Redmond, WA, USA). Both devices are self-expanding and are deployed under general anesthesia or sedation into segmental or subsegmental bronchi through a flexible or rigid bronchoscope using a catheter or guide wire.

Zephyr valves are made of a nitinol mesh covered by silicon, with a double silicon membrane inside that opens during expiration and closes during inspiration, a mechanism similar to Heimlich valves used for pleural drainage. Anchorage of the valve to the targeted bronchus is achieved via the irregular surface and self-expanding strength of the nitinol mesh.

The IBV valve is umbrella shaped and is made by a nitinol mesh covered by a polyurethane membrane. The valve is secured to the bronchial wall by hook-like anchors and can be removed by grasping and pulling on its proximal central rod with forceps. Both models are available in different sizes [133].

Following the first pilot studies [25, 29] on small number of patients documenting the safety and the feasibility of the procedures, few multicenter trials [32, 136, 137] have been performed with either device showing some beneficial effects lasting for up to 12 months in selected patients (Table 5).

Main complications related to use of valves entailed pneumonia in 3.6–4.2% of patients, pneumothorax in 4.2–4.5%, hemoptysis in 5.4–6.1%, and exacerbation of COPD in 7.9%.

So far there is no comparative study demonstrating the advantages of one model of valve over another. One potential advantage of valves is their easy removability after implantation.

The best clinical and functional results have been correlated with the development of lobar atelectasis. Unfortunately, atelectasis occurs in a minority of patients [133] probably due to the presence of collateral ventilation. In fact, collateral ventilation, which may be present physiologically but can be greatly increased in severely emphysematous lungs [138, 139], allows air to enter the treated lobe through communications present at the level of the interlobar fissure, potentially jeopardizing the efficacy of the valves.

The evaluation of collateral ventilation is thus a crucial step in selecting patients that might benefit from valve BLVR and integrity of the interlobar fissure evaluated by CT scan has been deemed a good predictor of the absence of collateral ventilation [140]. In addition, quantitative instrumental estimation of collateral ventilation can be now performed with the use of an endobronchial catheter system (Chartis System, Pulmonx Inc., Redwood, CA, USA) that can be inserted through a flexible bronchoscope [141].

In a study performed on 20 patients, the resistance measurements assessed by this device correlated with post-implantation atelectasis in 90% of cases [142]. Small pilot

TABLE 5: Results of bronchoscopic lung volume reduction.

Technique and first author	Treated patients (N)	Mortality (%)	Maximal follow-up (months)	FEV$_1$ (%increase)	FVC (%increase)	RV (%decrease)	6MWT (%increase)	Quality of life (SGRQ score decrease)
Valves (Zephyr)								
Sciurba [32]	220	0.9	6	4.3	NA	NA	2.5	2.8
Herth [136]	111	0.9	12	6	NA	NA	NB	NB
Valves (IBV)								
Sterman [137]	91	2.2	12	NB	NB	NB	5.9	8.7
Sealants								
Criner [33]	50 (28^L–22^H)	—	6	6.7–15.6	5.1–9.1	7.1–9.0	7–3.4	6.9–9–7
Herth [144]	21	—	6	11.4	15.5	NB	NB	7.5
Coils								
Slebos [145]	12	—	6	14.9	13.4	11.4	32.9	14.9
Vapor								
Snell [36]	11		6	NB	NB	NB	NB	15.3
Snell [146]	44	2	6	17	11	6	3	14
Airway Bypass								
Shah [149]	208	0.5	12	NB	NB	NB	NB	NB

COPD: chronic obstructive pulmonary disease; FEV$_1$: forced expiratory volume in one second; VC: vital capacity; RV: residual volume; 6MWT: 6-minute walking test; SGRQ: St.George questionnaire; NA: not assessed; NB: no benefit; ^{L}low dose; ^{H}high dose.

studies using this catheter system are currently ongoing to optimize the selection of patients for BLVR.

11.2. Devices Working at Lung Tissue Level

11.2.1. Sealants. First-generation sealants employed in BLVR were biological substances aimed at obtaining atelectasis and subsequent fibrosis of lung regions, thus realizing a so-called *biological lung volume reduction*. Early experimental and clinical pilot studies [28, 143] demonstrated the safety and the efficacy of the technique. Thereafter, a large multicenter phase-2 dose-ranging trial was conducted in 50 patients with heterogeneous upper-lobe predominant emphysema [33]. The treatment consisted of bronchoscopic instillation of fibrinogen and thrombin solution that polymerized in situ to form a hydrogel able to initiate a localized inflammatory reaction that collapsed the lung region over 4–6 weeks. Overall 26 patients underwent a single treatment session whereas 24, 2 sessions separated by 6–12 weeks.

At 12 weeks, in both groups there was a reduction in the RV/TLC and improvements in FEV$_1$, FVC, and 6MWT. However, 6 months after treatment, all the functional outcome measures remained significantly improved in the high-dose group only.

First-generation biological substances have now been replaced by a synthetic polymeric foam (Aeris Therapeutics, Woburn, MA, USA), which is injected into the peripheral airways and acts as a glue that seals the subsegmental target regions eventually leading to airway collapse and atelectasis.

In a multicenter study on 25 patients with severe heterogeneous emphysema, Herth et al. [144] instilled synthetic polymer sealant in a staged fashion within a 12-weeks period. After 24 weeks only the improvement in FVC was statistically significant. However, the results achieved in 14 COPD-stage-III patients were significantly better than those achieved in 11-stage IV patients in terms of improvement in FEV1 (16% versus 2%), FVC (24% versus 3%), RV/TLC (–7% versus –0.5%) and 6MWT (29 m versus 28 m).

There were no serious periprocedural complications or treatment-related deaths in this series. Minor adverse events included a "flu-like" reaction with elevated inflammatory markers, dyspnea, fever, and leukocytosis that were generally self-limited and resolved within 24–96 h. COPD exacerbations occurred after treatment in 10 patients.

Potential advantages of sealants over endobronchial valves include the easy feasibility and the alveolar rather than bronchial level of action, which should thus not be influenced by collateral ventilation. On the other hand, in contrast to endobronchial valves, use of sealants is not reversible and optimal patient and target site selection are therefore crucial. The procedure is deemed not indicated in presence of bullae greater than 15 cm in maximal size as well as in patients with lower-lobe predominant emphysema whereas applicability of this method in patients with homogeneous emphysema is not known [133].

11.2.2. Coils. Self-activating coils are placed into the airway to induce atelectasis and volume reduction by assuming their preformed coil shape and bending the airway and collapsing the surrounding lung tissue.

In a pilot study [144], coils (PneumRx, Inc.; Mountain View, CA) were bronchoscopically placed bilaterally into the most diseased areas of lungs to achieve BLVR.

Eleven patients, of whom 8 with homogeneous and 3 with heterogeneous emphysema, underwent 21 treatments with

a total of 101 coils placed. Adverse events included dyspnea in 10 instances, cough in 5 instances, COPD exacerbations in 3 instances, and chest pain in one. Improvements in FEV_1, RV, TLC, SGRQ, and 6MWT were observed at one and three months following the first procedure. The greatest relative changes were observed in 6MWT, SGRQ and dyspnea score in the patients with heterogeneous emphysema.

In a more recent study Slebos and coworkers [145] reported on 12 patients with severe heterogeneous emphysema who underwent a staged bilateral (8 patients) or a unilateral (4 patients) treatment. 216 coils were implanted with a median of 10 coils per procedure. At 6 months postprocedure, FEV_1, FVC, RV, 6MWT, and SGRQ improved significantly.

There were no life-threatening complications and adverse events included mild hemoptysis which occurred in 75% of the procedures, transient chest pain in 4 cases, and a spontaneously resolving pneumothorax in one case.

One theoretical advantage of coils over the use of valves is that they might confer benefit to patients with heterogeneous emphysema, independent of collateral ventilation. Potential disadvantages include uncertainty regarding removability of this devices long after deployment and the finding that an incompletely defined minimal amount of tissue is required for optimal performance of coils so that radiologic evidence of too severe emphysema or of giant bullae contraindicate the procedure [133].

11.2.3. Vapor Ablation.

Bronchial thermal vapor ablation (BTVA; Uptake Medical Corp., Seattle) involves the bronchoscopic application of thermal energy to targeted areas of emphysema. BTVA induced injury triggers an inflammatory response in the airway and lung tissue, which eventually result in BLVR. BTVA utilizes a vapor generator and metal balloon vapor catheter, with target dosing at 3–7.5 cal/g according to a prior CT based tissue-air algorithm [133].

In a pilot study by Snell et al. [36], 11 patients with heterogeneous emphysema underwent 9 right and 2 left upper lobe unilateral treatments with approximately 3 applications per lobe. Immediate mild opacification in the target areas was always demonstrated by chest X-ray and all patients could be discharged after 24–48 hours. Serious adverse events requiring hospitalization included COPD exacerbations in 2 patients whereas bacterial pneumonia, anxiety, and atrial tachycardia occurred in one patient each. Minor adverse events not requiring hospitalization included hemoptysis in 6 patient and inflammatory pneumonitis in 2.

All patients had an improvement in dyspnea at 3–16 weeks posttreatment. Amongst 7 patients who completed 1-month follow-up, the mean increase in FEV_1 was 9% and the decrease in RV was 7.4%. However, at 6 months there was no difference compared to baseline in FEV_1, FVC, and 6MWT. In contrast, dyspnea score and SGRQ improved both.

More recently, in a larger study, Snell and coworkers [146] reported on 44 patients with heterogeneous upper-lobe emphysema in whom a higher dose of vapor was administered (10 cal/g of lung tissue) and a total of 72 and 58 segments were treated in the right upper lobe and left upper lobe, respectively. At 6 months, there was a significant improvement in FEV_1, FVC, RV, 6MWT, SGRQ, and dyspnea index. After 6 months, the CT measurement of lobar volume was reduced by 48%. Lobar fissure integrity had no or minimal influence on overall results. Major adverse events included COPD exacerbations, pneumonia, respiratory tract infections, and hemoptysis which resolved with medical therapy, except for 1 patient who died secondary to a COPD exacerbation.

11.3. Airway Bypass.

The technique of airway bypass (Exhale Emphysema Treatment System, Broncus Technologies Inc., Mountain View, CA, USA) is based on the creation of extra-anatomic passages between the hyperinflated lung tissue and larger airways, with the aim of facilitating expiration and decreasing air trapping. The system is based on multiple components including a Doppler flexible probe with an ultrasonic transducer at its tip, to help identify blood vessel-free bronchial areas. Following some pilot studies, which demonstrated the safety of the technique, short-lasting improvement in functional parameters has been reported after the creation of bypasses in few studies [27, 147, 148]. Recently, Shah and coworkers [149] reported the results of a randomized, double-blind, sham-controlled study (EASE trial) on 315 patients with homogeneous emphysema and severe hyperinflation of whom 208 underwent airway bypass and 107 sham control. One patient died posttreatment due to massive hemoptysis. One month after treatment SGRQ score improved significantly but at 6 months no differences were seen between the study arms in FEV_1, FVC, RV, 6MWT, and SGRQ. Conclusion of the study was that airway bypass is unable to provide sustainable benefit in patients with severe homogeneous emphysema.

12. Future Perspectives

Data accumulated over the last two decades have definitively shown that LVRS can be highly effective in improving for up to several years respiratory function, exercise capacity, and quality of life in selected patients with severe emphysema.

Akuthota et al. [150] have recently noted that even when considering, as strict favorable markers for LVRS, the CT-based evidence of emphysema involving 40% or greater of the overall lung volume with a predominant upper-lobe distribution of disease, 15% of COPD patients with functional status staged as class III or IV according to the GOLD classification met criteria for LVRS. Nonetheless, despite a significant number of potential candidates, this surgical modality has progressively declined in use in the last years. Several conjectural reasons have been proposed to explain such an unexpected finding.

First, LVRS assessment has been perceived as overly complicated; second, many physicians are probably still unaware of the proper indications and benefits of LVRS; third, the NETT publication [49] reporting on the patient group at high risk for death with LVRS might have been misinterpreted as indicating generalized poor results for a high-risk procedure, and, finally, LVRS has been considered too costly [23, 151].

I would add that, at least in some instances, the availability of novel investigational BLVR methods, the efficacy of which is not yet proven, may have contributed to orient or possibly disorient the patients demand.

What clearly emerges from the literature is that the *Achilles heel* of LVRS is not attributable to doubts on clinical efficacy but rather to the significant perioperative morbidity of this treatment modality.

In this respect, I believe that the main triggering factors of LVRS-related morbidity include both adverse effects of general anesthesia with mechanical ventilation and the use of a resectional method entailing excision of wide portions of extremely fragile lung tissue [20].

As a result, further investigation aimed at developing less invasive strategies and methods that might allow to achieve long-term results as satisfactory as those shown by resectional LVRS but with a lower morbidity will be helpful.

In particular, a more thorough understanding of the pros and cons of a unilateral or staged bilateral LVRS strategy might contribute to reduce mortality and morbidity while assuring durable benefits.

Moreover, further results on use of novel options including the nonresectional LVRS method, which avoids any removal of lung tissue and can be performed in spontaneously ventilating subjects, as well as on the different novel BLVR methods that can be performed in a nearly ambulatory setting, are awaited and will be helpful to define a framework of alternative or complimentary treatment options.

Lung transplantation represents the only reliable therapy for a specific subset of patients as those with homogeneous emphysema associated with a too impaired respiratory function whereas in other instances it can represent a valid alternative to LVRS or can be included in a strategy, which combines both modalities.

Hopefully, the evolving scenario will prompt creation of noncompeting multidisciplinary teams including anesthesiologists, pulmonologists, radiologists, and thoracic surgeons, who will work together not only to optimize the results of LVRS but also to define by consensus, composite algorithms of treatment including different effective treatment methods.

13. Conclusion

This literature review indicates that LVRS is a highly effective palliative treatment modality for severe emphysema, particularly for those individuals who have CT evidence of heterogeneous upper-lobe predominant disease associated with impaired exercise capacity. By the application of different strategies of treatment including one-stage bilateral, unilateral and staged surgical approaches, significant and long-lasting improvements can occur in respiratory function, exercise capacity, and quality of life.

Mortality and morbidity of LVRS have been not negligible but novel surgical and BLVR methods are under active scrutiny and hold promise as reliably effective and as yet less invasive options.

Overall, it is worth noting that so far all novel investigative methods, even if based on different mechanisms of action, continue to respect an apparently paradoxical concept ideated more than 50 years ago [38], which suggested that patients suffering from the distressing effects of severe emphysema may greatly improve clinically and functionally by reducing their overall lungs' volume.

Such a genial concept warrants readily accepted, safely accomplished, well tolerated, and durably effective applicative methods.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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