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Lung Volume Reduction Surgery as a Bridge to Lung Transplantation

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Abstract

Lung volume reduction surgery (LVRS) improves lung function, exercise capacity, and quality of life in patients with advanced emphysema. In some patients with emphysema who are candidates for lung transplantation, LVRS is an alternative treatment option to lung transplantation, or may be used as a bridge to lung transplantation. Generally accepted criteria for LVRS include severe non-reversible airflow obstruction due to emphysema associated with significant evidence of lung hyperinflation and air trapping. Both high resolution computed tomography (CT) scan of the chest and quantitative ventilation/perfusion scan are used to identify lung regions with severe emphysema which would be used as targets for lung resection. Bilateral LVRS is the preferred surgical approach compared with the unilateral procedure because of better functional outcome. Lung transplantation is the preferred surgical treatment in patients with emphysema with α1 antitrypsin deficiency and in patients with very severe disease who have homogeneous emphysema pattern on CT scan of the chest or very low diffusion capacity.

Chronic obstructive pulmonary disease (COPD) due to emphysema is a progressive disease characterized by the destruction of the alveolar-capillary exchange units. It has been estimated that approximately 2 million individuals have emphysema.[1] Patients with moderate to severe emphysema typically experience exertional dyspnea, cough, and a gradual but progressive decline in exercise capacity.

Over the past several decades, despite significant advances in the care of patients with COPD, it remains a major cause of morbidity and mortality worldwide. For the majority of patients with mild to moderate emphysema, comprehensive medical management in conjunction with pulmonary rehabilitation, is often adequate to control symptoms, and to maximize exercise capacity.[1] However, for patients with advanced emphysema, standard medical therapy is often unsatisfactory. Until the reintroduction of lung volume reduction surgery (LVRS) by Cooper and colleagues,[2] lung transplantation was the only surgical treatment option available for patients with emphysema who remained symptomatic despite optimal medical care. Because some patients with advanced emphysema who are being evaluated for lung transplantation also fulfill the criteria for LVRS, and because of the scarcity of available donor lungs, LVRS has been suggested by some authors to serve as a bridge to lung transplantation.[3,4]

Since the reintroduction of LVRS 8 years ago, more is known regarding its short-term, and long-term effects on lung function and exercise performance. This review summarizes the most recent data regarding the short- and long-term outcomes of LVRS, the most current guidelines for optimal patient selection, and the role of LVRS as a bridge to lung transplantation.

1. Pathophysiological Basis for Lung Volume Reduction Surgery (LVRS)

COPD is characterized by peripheral airways inflammation,[5-7] resulting in lung parenchymal destruction and loss of alveolar-capillary units. Pathologically, the lung parenchymal destruction is typically seen as centrilobular emphysema, a process that denotes dilatation and destruction of the respiratory bronchioles. In milder forms of the disease, these lesions predominate in the upper lung regions, but may diffusely involve the entire lung in advanced disease.

The physiological effect of widespread parenchymal destruction due to emphysema is expiratory airflow limitation. Expiratory airflow limitation is due to the reduction in lung elastic recoil and decreased peripheral airway patency due to the loss of the tethering effect of the surrounding lung parenchyma. The consequence of expiratory airflow limitation is dynamic hyperinflation, air trapping, and the development of intrinsic positive end-expiratory pressure ($PEEP_i$). The resulting lung hyperinflation impairs respiratory muscle function and may also adversely affect cardiac function by limiting venous return and increasing right ventricular impedance. Moreover, ventilation-perfusion (V_A/Q) mismatch results in an elevation of physiologic deadspace, which further increases the patient's ventilatory load in order to maintain normal gas exchange.

Lung volume reduction surgery, as originally described by Brantigan and Mueller[8] in 1957, was conceived to reduce lung volume and reverse the physiological consequences of dynamic hyperinflation. Brantigan and colleagues hypothesized that in patients with severe emphysema and hyperinflation, downsizing the lungs would restore towards normal the outward radial traction on the small airways thereby facilitating expiratory airflow. In their surgical series, they reported subjective improvement in 75% of patients for periods of up to 5 years; however, the procedure was associated with a 16% postoperative mortality and no objective data were provided to supplement the subjective reports of patient improvement. Because of the high mortality and lack of objective data, Brantigan's procedure never gained full acceptance or widespread application.

In 1993, Cooper and colleagues[2] modified Brantigan's surgical technique. These modifications included median sternotomy, the use of a thoracic epidural catheter for postoperative pain control, and a cutting stapler reinforced with bovine pericardium to decrease postoperative air leaks. Preoperatively they used radiographic images, including computer tomography (CT) scans and quantitative lung perfusion scans, to help target for resection lung regions with the worst emphysema. In their initial report involving 20 carefully selected patients with emphysema who underwent bilateral LVRS via sternotomy, the mean improvement in forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were 82% and 27%, respectively. In their follow-up study on 150 patients the postoperative increases in FEV_1 and FVC, 6 months after LVRS, were reported as 51% and 20%, respectively.[9] Based on the favorable reports presented by Cooper and colleagues,[2] significant interest was rekindled in lung resection for severe emphysema. Soon after their initial report, a number of reports using unilateral or bilateral lung resections via median sternotomy, lateral thoracotomy or video-assisted thoracoscopic surgery (VATS) were reported from a number of different centers.[10]

Since then, several investigators have studied the different mechanisms of improvement in lung function and exercise capacity following LVRS. By decreasing lung volume, the overall effect of LVRS on the respiratory system is to improve lung mechanics. Specifically, LVRS increases lung elastic recoil and airway conductance leading to an improvement in expiratory airflow,[11,12] an increase in respiratory muscle strength,[13,14] a decrease in central respiratory drive,[15] and improvement in right ventricular function.[11,16]

2. Outcome of LVRS

In general, numerous published studies to date have shown that LVRS in carefully selected patients with diffuse emphysema leads to an improvement in lung function, exercise capacity and quality of life.[16-19] In addition, LVRS has also been shown to decrease the need for supplemental oxygen and corticosteroid therapy, and improve dyspnea.[16,20] The beneficial effects appear to peak at 3 to 6 months following LVRS, and are maintained for an additional 3 to 4 years followed by a gradual decline in lung function.[16,21,22]

The majority of studies that have reported the results of LVRS are limited by not being prospective, randomized, or controlled trials.[9,11,12] Recently, however, the results of two prospective, randomized, controlled trials[23,24] demonstrated that bilateral LVRS has a short-term beneficial effect on static lung function, exercise capacity, gas exchange, and quality of life, compared with optimized medical therapy, including pulmonary rehabilitation. However, the studies were limited by their small numbers, their short periods of observation (3 to 6 months), and the failure to characterize those patients who benefited from LVRS, compared with medical therapy alone.

2.1 Short-Term Results (Less Than 12 Months)

2.1.1 Spirometry

Early reports on physiological changes following LVRS focused on the improvement in lung function. In Cooper et al.'s[2] original series of 20 patients who underwent bilateral LVRS via median sternotomy, the mean improvement in FEV_1 and FVC was 82% and 27%, respectively. Because different investigators used different surgical techniques and applied different patient selection criteria, the reported magnitude of the increase in FEV_1 after surgery has been variable, and ranges between 13% to as high as 96%, compared with baseline. In one study, 34% of the patients who underwent bilateral LVRS via median sternotomy had less than a 20% improvement in FEV_1, 3 to 6 months after surgery.[25] Table I summarizes postoperative changes in spirometry reported in published studies.

Several factors may contribute to the variability in improvement in spirometry after LVRS. Several preoperative factors

Table I. Short-term changes in spirometry, lung volumes, diffusion capacity, and gas exchange after bilateral lung volume reduction surgery (reproduced from Flaherty and Martinez,[26] with permission)

Author	Procedure	No. of patients/ follow-up (months)	FEV_1 (% change)	FVC (% change)	RV (% change)	TLC (% change)	D_{LCO} (% change)	PaO_2 (Δ mm Hg)	$PaCO_2$ (Δ mm Hg)
Cooper et al.[2]	MS	20/20	82	27	–39	–22	NA	6	–1
Argenziano et al.[27]	MS and thoracosternotomy	85/51	58	41	NA	NA	NA	NA	NA
Bingisser et al.[28]	VATS	20/20	42	29	–23	–16	NA	4	–2
Daniel et al.[29]	MS	26/17	49	23	–14	–14	NA	4	–2
Gaissert et al.[30]	MS	33/33	85	NA	NA	NA	NA	–6	–5
Gelb et al.[12,18]	VATS	12/12	68	18	–30	–18	196	NA	NA
Kotloff et al.[25]	MS	80/56	41	20	–28	NA	NA	NA	NA
	VATS	40/34	41	25	–23				
Benditt et al.[19]	MS	21/21	30	17	–22	–7	NA	5	–4
Brenner et al.[31]	VATS	145/130	62	40	–28	–19	63	–1	–1
Bousamra et al.[32]	MS[a]	45/37	59	37	NA	NA	NA	NA	NA
Cordova et al.[16]	MS	69/25	37	22	–27	–11	14	NA	–2
Martinez et al.[33]	MS	17/17	38	17	–25	–13	10	NA	NA
Stammberger et al.[34]	VATS	42/36	43	18	–13	–2	NA	7	–2
Weder et al.[35]	VATS	50/50	34-81	34-60	–20 to –30	–9	NA	4 to 7	–2 to –4
Wisser et al.[36]	MS	15	60	33	–22	–11	NA	3	–6
	VATS	15	62	35	–29	–8		3	–1
Albert et al.[37]	MS	46/46	33	52	–22	–10	24	3	–3
Ferguson et al.[38]	MS	27/18	32	14	–28	–15	–4	1	–3
Hazelrigg et al.[39]	MS	29	40	NA	–28	NA	15	9	–1
	VATS	50	41		–37		10	2	–5
Ingenito et al.[40]	VATS	29/29	33	18	NA	NA	NA	NA	NA
Ko & Waters[41]	MS	19	28	NA	–7	NA	NA	11	–1
	VATS	23	62		–11			–2	–9
Norman et al.[42]	MS	14/14	26	11	–27	–16	NA	1	0
Scharf et al.[43]	MS	9/9	61	30	–35	–13	18	NA	NA
Stammberger et al.[44]	VATS	40/40	55	42	–25	–17	0	6	–3
Tschernko et al.[45]	VATS	8/8	38	24	–28	–9	NA	NA	NA
Anderson[46]	MS	80/20	21	NA	NA	NA	NA	NA	NA
Thurnheer et al.[47]	VATS	70/70	23-57	17-47	–15 to –28	–6 –18	–2 to 5	5	–2 to –3

a 42 patients had median sternotomy.

D_{LCO} = lung diffusion capacity for carbon monoxide; **FEV_1** = forced expiratory volume in 1 second; **FVC** = forced vital capacity; **MS** = median sternotomy; **NA** = not available; **$PaCO_2$** = partial pressure of carbon dioxide; **PaO_2** = arterial partial pressure of oxygen; **RV** = residual volume; **TLC** = total lung capacity; **VATS** = video-assisted thoracic surgery.

have been suggested as important in predicting the magnitude of improvement in spirometry after LVRS. These factors include the pattern of distribution of emphysema as viewed on the high resolution CT scan of the chest,[36] the extent of air trapping as measured by residual volume (RV)/total lung capacity (TLC),[48] the type of surgical techniques utilized[49] and whether unilateral or bilateral LVRS was performed.[50] Each of these factors will be discussed separately in the subsequent sections.

2.1.2 Lung Volumes

The extent of the reduction in lung volume after surgery depends to a certain extent on the amount of lung tissue resected and the surgical techniques utilized. On average, TLC and RV are reduced by 10 to 20% and 15 to 30%, respectively, at 3 to 6 months after bilateral LVRS. However, the reported decreases in lung volume are variable as shown in table I. In general, decreases in TLC and RV following bilateral LVRS are greater following bilateral, stapled LVRS compared with unilateral, or laser surgical resection.[10,50]

2.1.3 Diffusion Capacity

The effect of LVRS on diffusion capacity (D_{LCO}) has not been consistently reported in the majority of studies. Some studies reported a slight increase in D_{LCO}[12,39] while others showed no significant change after surgery.[16,23] In an animal model of emphysema, the D_{LCO} decreased in proportion to the amount of lung tissue removed. In a recent report from the National Emphysema Treatment Trial, patients who underwent bilateral LVRS who had a preoperative D_{LCO} less than 20% of predicted, and an FEV_1 less than 20%, had a 30-day mortality rate of 16% compared with no deaths over the same time period in patients who were treated medically.[51] In addition, these patients with very severe emphysema with very low diffusion capacity did not experience a significant physiological improvement following LVRS. In essence, patients with very severe emphysema and homogeneous emphysema should be referred for lung transplantation.

2.1.4 Arterial Blood Gas

The initial report on the effect of LVRS on gas exchange showed a modest increase in the partial pressure of oxygen in the arterial blood (PaO_2) and a decrease in the partial pressure of carbon dioxide ($PaCO_2$). Cooper and colleagues[2] showed an increase in PaO_2 from a baseline value of 64 to 70mm Hg with no significant change in $PaCO_2$ at 6 months post-surgery in their first 20 patients. In their subsequent report of 101 patients, the PaO_2 increased by a mean of 8mm Hg after surgery, while the mean $PaCO_2$ also decreased by 4mm Hg.[9] Other investigators have since reported similar improvements in arterial blood gases after surgery.[20,28,52,53] However, some authors reported contradictory responses in arterial blood gases post-LVRS characterized by a significant increase in PaO_2 without changes in $PaCO_2$[54,55] or *vice versa*, that is, no significant post-operative changes in PaO_2, but a modest decrease in $PaCO_2$.[11,38,56,57]

The conflicting reports by different centers on the effect of LVRS on gas exchange is unclear, but are likely to be multifactorial and related to differences in patient selection, surgical techniques, and variabilities in measuring PaO_2 in patients receiving supplemental oxygen via nasal cannula.

2.1.5 Oxygen Requirement

Some studies have reported a reduction in the requirement for supplemental oxygen use after LVRS. Three to six months after LVRS, several studies have reported a reduction in the number of patients requiring supplemental oxygen, anywhere from 16 to 42%.[2] In 101 patients who underwent bilateral LVRS who were followed up for at least 1 year, the number of patients who required long-term supplemental oxygen at rest decreased from 52 to 16% at 6 months after surgery.[9] To a lesser degree, LVRS also decreased the number of patients who required supplemental oxygen during exercise from 92% before surgery to 44% at 6 months post-surgery. In 56 patients from the same report who were followed up to 1 year post-surgery, the majority of the patients who were successfully weaned from supplemental oxygen were able to maintain an oxygen free status.[9]

In a study designed to assess oxygen requirement during exercise before and after LVRS using standard criteria for the use of supplemental oxygen, Bousamra and colleagues[32] showed that in their series of 45 patients (bilateral 43), oxygen requirements during exercise were essentially unchanged after LVRS. Interestingly, 10 of their patients stopped using oxygen because of deceased dyspnea, despite documented oxygen desaturation during exercise. More data are needed to determine the actual percentage of patients who have a reduction in need for supplemental oxygen post-LVRS, both at rest and during exercise, and to assess the durability of the response over time.

2.1.6 Six-Minute Walk Test

The improvement in exercise capacity is one of the most important outcome measures reported in LVRS studies. The 6-minute walk test, a timed measure of distance walked, is commonly used as a simple, reproducible measure of functional capacity. In general, the distance walked in 6 minutes is significantly increased at 3 to 6 months after LVRS. The average reported percentage increase in the 6-minute walk distance ranged from 15 to 103%, as shown in table II. The extent of the contribution of pulmonary rehabilitation to increases in the 6-minute walk distance, independent of LVRS, is unclear in some of the reported studies. Results from prospective, randomized,

Table II. Changes in cardiopulmonary exercise capacity after lung volume reduction surgery (reproduced from Flaherty and Martinez,[26] with permission)

Author	No. of patients	6-minute walk test (% change)	Maximal work (% change)	$\dot{V}O_{2max}$ (% change)	$\dot{V}_{Emax}$ (% change)	$\dot{V}_{Tmax}$ (% change)	F_b (% change)
Bingisser et al.[28]	20	59[a]	52	30	31	NA	NA
Benditt et al.[19]	21	NA	46	25	27	43	0
Cordova et al.[16]	25	35	48	25	29	34	–12
Keller et al.[55]	25	15	41	22	17	20	–4
Martinez et al.[33]	17	103	NA	NA	NA	2	–22
Wisser et al.[36]	30	NA	28	NA	NA	NA	NA
Criner et al.[13]	20	20	33	37	38	19	–13
Ferguson et al.[38]	27	18	20	3	30	25	4
Stammberger et al.[44]	40	52	43	28	31	39	–4
Tschernko et al.[17]	8	NA	100	27	NA	25	–15

a 12-minute walk distance.

F_b = respiratory rate; **NA** = not available; **$\dot{V}_{Emax}$** = maximum minute ventilation; **$\dot{V}_{Tmax}$** = maximum tidal volume; **$\dot{V}O_{2max}$** = maximum oxygen consumption.

controlled trials reported to date show that the improvement in the 6-minute walk test after LVRS is independent of pulmonary rehabilitation. Criner and colleagues[23] showed a significant increase in 6-minute walk distance (337 + 99 *vs* 282 + 100m; $p \leq 0.001$) in patients who underwent bilateral LVRS via median sternotomy compared with intensive pulmonary rehabilitation alone. In the study by Geddes et al.,[24] the median shuttle walk distance increased by 50m in the surgical group and decreased by 20m in the medical group.

2.1.7 Cardiopulmonary Exercise Test

An increase in exercise capacity after LVRS reflected by the 6-minute walk test, is supported by similar improvements reported during cardiopulmonary exercise testing. Several authors have shown that maximum oxygen consumption ($\dot{V}O_{2max}$), total exercise time, maximum workload, and maximum minute ventilation ($\dot{V}_E$) are significantly increased 3 to 6 months after unilateral,[55] or bilateral LVRS[19,23,38] (table II). In addition, the increase in $\dot{V}_E$ at a given workload is mainly achieved by an incremental increase in tidal volume with only a minimal increase in respiratory rate.[23,38] The increase in exercise capacity is due mainly to increases in maximum ventilation and resting ventilatory reserve which is thought to be due in part to increases in inspiratory and expiratory flow both at rest, and during exercise.[16,38] This favorable ventilatory pattern during exercise also leads to a decrease in dead space ventilation during exercise.[38] Stammberger and associates[44] showed that the increase in $\dot{V}O_{2max}$ and $\dot{V}_{E\,max}$ after LVRS correlates with increases in FEV_1 and the decreases in hyperinflation as measured by RV/TLC. Additionally, LVRS may also improve exercise performance by favorably improving cardiac function. After LVRS, the heart rate is lower at a given workload and the oxygen pulse is higher compared with baseline, suggesting an improvement in ventricular function due to a lower end-expiratory lung volume, and autopeep, and possibly a decrease in pulmonary vascular resistance.[16,19]

Overall, the improvement in exercise capacity after LVRS is most likely due to a combination of an improvement in expiratory airflow, reduction in the degree of hyperinflation, improvement in respiratory muscle function and possibly, in cardiac function as well.

2.1.8 Dyspnea

Several investigators have reported a significant decrease in dyspnea after both unilateral, and bilateral LVRS.[9,20,29,33] However, bilateral LVRS appears to be superior in decreasing exertional dyspnea compared with the unilateral procedure. McKenna and associates[58] showed that the percentage of patients undergoing unilateral LVRS who complained of dyspnea with mild exertion [higher Medical Research Council (MRC) dyspnea score; 3 = stops for breath every few minutes; 4 = housebound] decreased from 73 to 44% postoperatively, whereas only 12% of patients who underwent bilateral LVRS experienced the same degree of dyspnea after surgery. In this study, patients who had bilateral LVRS had higher increases in FEV_1 compared with unilateral LVRS, suggesting perhaps that a higher gain in lung function could account for superior symptomatic relief from disabling dyspnea after bilateral LVRS, compared with the unilateral procedure. However, in the study by Brenner et al.,[31] a weak correlation existed between changes in FEV_1 and the dyspnea index after LVRS. Indeed, 10 of 37 patients who had minimal, or no improvement in FEV_1, exhibited significant decreases in the MRC scale of dyspnea (less dyspneic) post-LVRS. Martinez and colleagues[33] also reported similar observations. In 17 patients who showed a significant improvement in dyspnea, 6 patients had a less than 20% improvement in FEV_1 after bilateral LVRS. This observation suggests that the improvement in dyspnea after

LVRS is likely to be multi-factorial, and not only due to an increase in expiratory airflow alone. Other physiological changes following LVRS such as a decrease in hyperinflation, an increase in respiratory muscle strength, and a decrease in respiratory drive may all contribute to a decrease in dyspnea on exertion.

2.1.9 Quality of Life

The short-term effect of LVRS on quality of life, using either disease specific health questionnaires, or general health-related quality-of-life measures have been reported by several investigators.[9,16,59] In Cooper et al.'s[2] initial reports of 20 patients, and in a subsequent report of 150 patients who underwent bilateral LVRS, both the Survey-Short Form 36 (SF36) and Nottingham Heath Profiles showed significant improvement, 6 months post-LVRS. Hazelrigg et al.[39] showed a similar improvement in quality of life following both staged thoracoscopy and median sternotomy. The improvement in social functioning has been correlated with spirometric improvement, and the improvement in exercise capacity has shown to correlate with an improvement in physical functioning.[38] Moreover, the improvement in Sickness Impact Profile (SIP) scores was associated with a reduction in hyperinflation, possibly resulting in a more efficient pattern of breathing and dyspnea.[60]

2.2 Long-Term Results (Exceeding 12 Months)

2.2.1 Spirometry

Because emphysema is a slowly progressive disease, serious concerns on the effect of LVRS on the rate of decline of FEV_1 have been raised by some investigators. In the study by Brenner et al.,[22] the highest rate of decline in FEV_1 was seen in patients who experienced the greatest improvement in FEV_1 during the initial 6 months after surgery. Those patients who had the least improvement in FEV_1 after surgery had the lowest rate of decline.

To date, only few published studies have addressed the long-term stability of lung function after LVRS. In our report, 13 patients who underwent bilateral LVRS via median sternotomy had increases in FEV_1 3 months after LVRS that were sustained at 12 months of follow up. In 6 of 13 patients with data at 18 months post surgery, the FEV_1 remained higher compared with baseline (0.91+ 0.37*vs* 0.69 + 0.02L; $p < 0.12$).[16] Gelb and colleagues[18] showed similar sustained improvements in FEV_1 and FVC at 12 months post-surgery when compared with baseline data. However, both FEV_1 and FVC 12 months post-LVRS were significantly lower when compared with 6 months post-LVRS suggesting that the improvement in lung function post-LVRS peaks at 6 months. More recently, the same group of investigators reported lung function in 26 patients 5 years after bilateral LVRS via video-assisted thoracoscopy.[21] An increase in FEV_1 >200ml or FVC >400ml at 1, 2, 3, 4, and 5 years after LVRS were seen in 73%, 46%, 35%, 27%, and 8% of patients, respectively. The annual rate of decline in FEV_1 was 141 ± 60 ml/year with the fastest rate of decline in the initial 1 to 2 years post-LVRS. In the author's analysis, only the preoperative FVC separated those patients who achieved significant long-term improvement beyond 3 years. Thus, it appears that the improvement in lung function is maintained for 3 to 4 years post-LVRS in some patients.

The long-term effects of LVRS on patients with cigarette-induced emphysema do not seem to apply to patients with emphysema due to $\alpha 1$ antitrypsin deficiency. In a study by Cassina et al.,[61] the physiological outcome of 12 patients with $\alpha 1$ antitrypsin deficiency and 18 patients with smoking-related emphysema were compared following bilateral targeted LVRS. After LVRS, both groups of patients showed significant short-term improvements in dyspnea score, 6-minute walk test and pulmonary function tests. However, the improvements in lung function in the $\alpha 1$ antitrypsin deficiency group returned to baseline at 6 to 12 months after LVRS. Moreover, the FEV_1 decreased further at 24 months despite optimal medical therapy. These data suggest that patients with severe emphysema due to $\alpha 1$ antitrypsin deficiency will only most likely have short-term benefit from LVRS and should instead undergo lung transplantation.

2.2.2 Lung Volumes

The decrease in RV and TLC post-LVRS appear to be maintained for at least 2 years. Cooper et al.,[9] showed that the initial decreases in RV and TLC reported in their first cohort of 20 patients were maintained at 2 years after LVRS. Similarly, we showed a sustained decrease in lung volumes in 6 patients with 18 months of follow-up.[16] Gelb and associates[62] showed similar sustained decreases in RV and TLC at 2 years in 12 patients who underwent bilateral LVRS via video-assisted thoracoscopy. However, at 3 years after LVRS, the same authors showed that not all patients exhibited sustained decreases in lung volumes; only 9 of 26 patients had significantly lower RV and TLC at 3 years post-LVRS.[63] In ten short-term responders (<2 years) who died, RV and TLC reverted to preoperative values.[63] Thus, similar to spirometric data, sustained decreases in lung volumes occur in only some, but not all patients at 3 to 4 years post-LVRS.

2.2.3 Diffusion Capacity

Limited data are available regarding the effects of LVRS on diffusion capacity during long-term follow-up. In 12 patients followed up to 24 months post-LVRS, the diffusion capacity at 2 years remained significantly higher compared with the preoperative value (43 *vs* 18% of predicted; $p < 0.001$).[62] In 9 patients who were considered long-term responders, the diffusion capacity/alveolar volume ratio remained significantly higher compared with baseline.[63]

2.2.4 Gas Exchange and Oxygen Requirements Post-LVRS

In studies that showed initial significant increases in PaO_2 and decreases in $PaCO_2$ after LVRS, very little data has been published regarding its long-term stability. In 18 patients who underwent bilateral LVRS via thoracoscopy, the measured PaO_2 at baseline, 3 months, and 24 months were 63.3 + 2.6, 70.1 + 2.7, and 64.7 + 3.1mm Hg, respectively.[64] The short-term increase in PaO_2 at 3 months was no longer seen at 2 years after LVRS. Similar decreases in PaO_2, to near the baseline values, was reported by Gelb and associates[62] in 12 patients at 24 months following bilateral LVRS via thoracoscopy.

Similar long-term changes in $PaCO_2$ have been reported after LVRS. The initial decreases in $PaCO_2$ at 3 months post-LVRS was lost at 24 months follow-up, although patients with markedly heterogeneous emphysema were likely to maintain decreases in $PaCO_2$ at 24 months, compared with patients with homogeneous emphysema.[64]

As expected, the need for supplemental oxygen depends on the magnitude of increase in PaO_2 after LVRS. In Cooper et al.'s[2] initial cohort of 20 highly selected patients, 26% required long-term oxygen therapy at baseline compared with zero patients at 12 and 24 months after bilateral LVRS. However, the number of patients who required supplemental oxygen during exercise increased from 5% at 12 months to 32% at 24 months.[2] Beyond 2 years, an increasing number of patients required supplemental oxygen. In 18 of 26 patients who were oxygen dependent preoperatively, 78%, 50%, 33% and 22% of patients were weaned from oxygen therapy at 1, 2, 3, 4 years, respectively, after LVRS.[21]

2.2.5 Six-Minute Walk Test

There are few data available regarding the long-term stability in exercise performance after LVRS. The initial increase in 6-minute walk distance seen at 3 to 6 months appears to be maintained at 2 years post-LVRS despite a slight downward trend in FEV_1.[9] We similarly showed sustained increases in 6-minute walk distance in 12 patients at 12 months, and in 6 patients at 18 months after bilateral LVRS via sternotomy.[16] Hamacher and colleagues[64] showed similar sustained improvements in 6-minute walk distance at 24 months post-LVRS in patients with heterogenous emphysema who underwent bilateral LVRS via thoracoscopy. Interestingly, in patients with α1 antitrypsin deficiency, the 6-minute walk distance at 24 months follow-up remained significantly higher compared with the preoperative value despite an FEV_1 that was lower than baseline.[61]

2.2.6 Cardiopulmonary Exercise Test

Symptom-limited cardiopulmonary exercise is a better measure of exercise capacity since it does not have the inherent limitations of the 6-minute walk test. Firstly, the protocol of performing the 6- minute walk test is not well standardized across various studies. In addition, the 6-minute walk test is subject to a learning effect, that is, patients are able to walk more efficiently with repeated testing even without a specific intervention being conducted. Unfortunately, long-term data on the stability of cardiopulmonary exercise are limited. In 12 patients followed up to 12 months after bilateral LVRS via median sternotomy, total exercise time, $\dot{V}O_{2max}$, $\dot{V}_{Emax}$, and tidal volume at peak exercise remained higher compared with baseline values; however, there was a downward trend in $\dot{V}_{Emax}$ at 12 months and of $\dot{V}O_{2max}$ starting at 6 to 12 months.[16] Gelb and associates[62] showed a similar downward trend in exercise capacity in 7 patients at 24 months after bilateral LVRS via thoracoscopy. At 24 months follow-up, only $\dot{V}O_{2max}$ remained significantly higher compared with baseline, while $\dot{V}_{Emax}$ and $\dot{V}_{Tmax}$ drifted down to preoperative values. At 36 months follow-up, only 9 of 26 (35%) patients showed a persistent improvement in exercise capacity. At 5 years post-LVRS, only 2 of 26 patients showed a sustained clinical benefit from LVRS.[21]

2.2.7 Dyspnea and Quality of Life

Similar to the declines reported in lung function and exercise capacity over time, the decrease in dyspnea after LVRS also wanes over time, but not necessarily in tandem with the decrease in lung function. Using the Fletcher Scale, 12 of 13 patients had an improvement in dyspnea following LVRS (11 unilateral, 2 bilateral). At 2-year follow-up, only 4 of 12 patients continued to enjoy symptomatic relief from dyspnea. No patients maintained an improvement in dyspnea at 48 months follow-up.[53] Gelb et al.[21] reported a greater than 1 grade decrease in dyspnea score at 6 months post-LVRS in 26 patients with severe emphysema who underwent bilateral LVRS via video-assisted thoracoscopy. At 2, 3, 4, and 5 years follow-up, only 69%, 46%, 27%, and 15% of patients, respectively, were able to maintain an improvement in dyspnea.

3. Patient Selection

In most reported case series, only about 20 to 25% of patients with severe emphysema who are referred for surgery are deemed to be good LVRS candidates after preoperative evaluation. Despite numerous published reports in the literature, there are no established inclusion and exclusion criteria. More recently, the National Emphysema Treatment Trial released its preliminary analysis in 1033 patients who had been randomized to receive

Table III. Commonly used preoperative diagnostic tests for lung volume reduction surgery

Pulmonary assessment
Spirometry
Lung volume measurements
Diffusion capacity
Arterial blood gas
6-Minute walk test
Cardiopulmonary exercise test
Assessment of the distribution of emphysema
Chest radiograph
High resolution computer tomography of the chest
Quantitative lung ventilation/perfusion scan
Cardiac evaluation
Electrocardiogram
Cardiac echocardiogram
Dobutamine-radionuclide cardiac scan if indicated
Right and left heart catheterization (selected patients)

LVRS or medical therapy.[51] In 69 patients who had an FEV_1 less than 20% of predicted, with either a homogeneous distribution of emphysema on high resolution CT of the chest (chest CT), or carbon monoxide diffusing capacity ≤20% of the predicted value, the 30-day mortality after surgery was 16%, compared with a mortality of 0% in the medically treated patients ($p < 0.01$). In patients who had all 3 high risk characteristics (e.g. D_{LCO} <30% of predicted, severe diffuse homogeneous pattern of emphysema on chest CT, and FEV_1 ≤20% of predicted), the 30-day mortality rate following LVRS was even higher at 25%.

These data suggest that patients who meet the above profile are not suitable candidates for LVRS, because they are at high risk of death, and even if they do survive, they are unlikely to receive significant physiological or functional benefit. Following this report, the National Emphysema Treatment Trial has been modified to exclude future patients exhibiting these characteristics from enrolling into the trial. Additional exclusion criteria include age >75 years, tobacco usage within 6 months prior to evaluation, evidence of hypercapnia ($PaCO_2$ >55mm Hg) and moderate to severe pulmonary hypertension (mean pulmonary artery systolic pressure >50mm Hg), underlying cardiac dysfunction, or other significant comorbid medical problems that affect survival. Patients who are obese (bodyweight >125% of predicted ideal bodyweight), undernourished (bodyweight <75% of predicted ideal bodyweight), and who are ventilator dependent were also similarly excluded.

Overall, patients who are considered for surgery should have baseline testing that should include at least pulmonary function tests and radiographic evidence of end-stage emphysema. This means that the pulmonary function testing should show evidence of severe non-reversible airflow obstruction with a FEV_1 in the range of 20 to 35% of predicted; evidence of hyperinflation and air trapping should also be present as shown by TLC ≥100% of predicted and RV ≥150% of predicted. The chest radiograph and high resolution CT should demonstrate parenchymal emphysematous changes and hyperinflation. A quantitative ventilation and perfusion scan is used to quantify variable regions of perfusion within each lung field, and in conjunction with a chest CT scan, is used to identify lung regions with severe emphysema which would be used as targets for lung resection. Preoperative testing commonly used to evaluate potential LVRS candidates is shown in table III.

4. Preoperative Predictors of LVRS Outcome

In general, patients with emphysema who appear to achieve good results from LVRS have the following characteristics: heterogeneous bullous changes within the lung on CT scan; presence of severe hyperinflation and air trapping; absence of severe hypercapnia and pulmonary hypertension; and the ability to participate in outpatient pulmonary rehabilitation. As previously discussed, patients with very severe emphysema characterized with an FEV_1 <20% of predicted, diffusion capacity of <20%, and homogeneous pattern of emphysema on chest CT scan should undergo lung transplantation as the preferred surgical procedure. Additionally, preoperative hypercapnia of ≥45mm Hg and 6-minute walk test performance ≤200m either pre- or post-rehabilitation has been shown to be strong predictors of increased mortality after LVRS.[65] However, patients with mild to moderate hypercapnia alone should not be excluded for LVRS. Although hypercapnic patients had a lower preoperative FEV_1, D_{LCO}, a PaO_2/F_iO_2 ratio and 6 minute walk distance compared to normocapnic patients, the percentage of improvements in FVC, FEV_1, TLC, RV, RV/TLC were comparable to eucapnic patients. Moreover, there were no differences in morbidity and mortality between the hypercapnic and eucapnic COPD patients.[57,66]

One of the reasons for the wide range of improvement in pulmonary function studies that have been published to date is the variability in the pattern and distribution of emphysema. Several reports have shown that morphological grading of the distribution of emphysema by CT scan may help predict the extent of improvement in expiratory airflow following LVRS.[36,50,67]

5. Surgical Approaches in LVRS

A variety of surgical techniques have been used in LVRS. These techniques include median sternotomy with bilateral stapling resection, video-assisted thoracoscopic surgery (VATS) performed unilaterally, or bilaterally with stapling lung resection, and unilateral VATS with laser ablation of emphysematous tissue. As previously mentioned, the goal of LVRS is targeted resection of 30 to 40% of the severely emphysematous lung as identified on the preoperative CT scan, quantitative V/Q scan, as well as intraoperative findings.

The type of surgery whether median sternotomy versus VATS depends largely on the surgical preference of individual surgeons and the availability of surgical expertise within institutions. Bilateral LVRS whether performed via median sternotomy, or VATS, leads to similar improvements in lung function and exercise capacity, although VATS may be associated with lower postoperative morbidity and mortality.[25] Laser surgery is not recommended for LVRS because of less than satisfactory results compared with stapled resection. In a study by McKenna and coworkers[49] comparing the efficacy of neodymium-yttrium aluminum garnet (Nd-YAG) contact laser surgery with stapled lung resection in 72 patients who underwent unilateral LVRS, there was no difference in postoperative morbidity and mortality between the 2 groups. However, patients who underwent stapled lung surgery had a significantly higher improvement in lung function compared with the laser ablation group (FEV_1: 33 *vs* 13%).

5.1 Bilateral versus Unilateral LVRS

In appropriately selected patients, bilateral is preferred over unilateral LVRS because of a greater improvement in postoperative lung function with comparable perioperative mortality.[10] More importantly, bilateral LVRS via VATS appears to have a better 2-year survival compared with unilateral LVRS. In a study of 260 patients with COPD who underwent LVRS via VATS (bilateral VATS, n = 159; unilateral VATS, n = 101) overall survival at 2 years was 86.4% after bilateral LVRS compared with 72.6% in patients who underwent unilateral LVRS (p = 0.001).[68] However, another study showed no survival advantage in patients who underwent bilateral compared with unilateral LVRS.[69] Presently, because of better functional outcome in patients who underwent bilateral compared with unilateral LVRS, bilateral LVRS is the preferred surgical approach. Unilateral LVRS should only be considered in patients with asymmetric emphysema distribution, and pleural adhesions from prior thoracic surgery.[27]

6. Morbidity and Mortality

The mortality rates post-LVRS range from as low as 0% to as high as 23%. In carefully selected patients and with an experienced surgeon, the postoperative mortality rate is approximately 5%. The causes of postoperative complications and mortality are shown in table IV. Common postoperative complications after LVRS are air leak, pneumothorax, post-operative respiratory failure, and nosocomial pneumonia. Recently, postoperative gastrointestinal complications have been reported as a potential serious complication following LVRS.[70] Diabetes mellitus, anemia, perioperative use of corticosteroids and parenteral meperidine (pethidine) have been identified as predictors of serious gastrointestinal complications after LVRS.

Table IV. Common causes of post-operative morbidity and mortality in 343 patients following bilateral thoracoscopic lung volume reduction surgery (LVRS) [reproduced from Naunheim et al.,[69] with permission from the Society of Thoracic Surgeons (The Annals of Thoracic Surgery 1999; 68: 2026-32)]

Complication	Patients (%)
Air leak	68
Pneumonia (%)	14
Gastrointestinal complications	8.3
Tracheostomy	6.2
Arrhythmia	8.9
Heimlich valve at discharge	6.0
Reoperation for bleeding	3.1
Operative mortality	
Respiratory failure	2
Cardiac related	1.5
Sepsis	0.9
Multi-organ failure	1.2
Pneumonia	0.9

The type of operative technique may influence the incidence of post-operative complications. In a study 136 patients underwent bilateral LVRS either via median sternotomy (MS group, n = 86) or via thoracoscopic approach (VATS group, n = 50; staged procedure, n = 12). The MS patients were older compared with the VATS group (63.9 + 6.8 *vs* 59.3 + 9.4, p < 0.005), but were otherwise equally matched for severity of emphysema and functional impairment. Patients who had bilateral LVRS via median sternotomy had more life threatening complications (22.1 *vs* 6%, p = 0.01) after surgery compared with VATS patients. Moreover, MS patients were likely to be reintubated after the surgery, had a longer intensive care unit stay and were more likely to require tracheostomy.[71]

The long-term survival of 673 patients from multiple centers in the US after bilateral or unilateral LVRS via VATS was 73% at 3 years.[69] In a separate report of 22 patients who were deemed to be good candidates for LVRS, but were denied insurance coverage for the procedure by medicare, the 3-year survival was 64%.[72] Thus, it appears that LVRS may not only improve exercise capacity and quality of life in patients with advanced emphysema, but may also have a favorable impact on long-term survival. A definitive conclusion on the effect of LVRS on long-term survival will have to await the results of the National Emphysema Treatment Trial.

7. LVRS as a Bridge to Lung Transplantation

Some patients with COPD who are being evaluated for lung transplantation are also appropriate candidates for lung reduction surgery. Thus, LVRS may be used as a 'bridge' to lung transplantation in patients who have rapidly deteriorating lung function or to supplant lung transplantation as a procedure of choice in some patients who do not wish to take immunosuppression medications. Because COPD is the most common diagnosis in patients who undergo lung transplantation, successful LVRS in select patients with advanced emphysema may allow transplant centers to channel available donor organs to other sicker patients who are at risk of dying during the waiting period. Other potential benefits may include a shorter waiting period (currently 18 to 24 months) due to less patients with COPD actively awaiting transplantation. From the patient's perspective, successful LVRS may obviate the need for immunosuppression, and its constant risk of opportunistic infections.

The question of which group of patients with COPD awaiting lung transplantation will benefit from LVRS, and which group of these patients will do poorly after LVRS and therefore be better served by lung transplantation as the initial procedure is unclear. In most transplant centers, prior thoracic surgery is not a contraindication to lung transplantation.

In a study from the University of Pittsburgh involving 95 patients with end-stage emphysema who were evaluated for lung transplantation, 45 (47%) patients met the criteria for both lung transplantation and LVRS.[73] Thirty of these 45 patients underwent LVRS. Three months after LVRS, the group as a whole showed significant increases in FEV_1, maximum voluntary ventilation, and a significant decrease in hyperinflation and air trapping. However, in a subgroup analysis performed by the authors, 20 patients (group A) had a greater improvement in static lung function and exercise capacity compared with the remaining 10 patients (group B) who had suboptimal improvement in lung function 3 months after LVRS. Analysis of the different preoperative data and surgical techniques suggest that unilateral LVRS and hypercapnia may be a predictor of suboptimal outcome following LVRS in this patient population. A subsequent study by the same authors showed that LVRS is an effective palliative alternative to lung transplantation in 75% of carefully selected patients with emphysema with durable improvement in lung function up to 32 months of follow up.[3]

In a similar study evaluating the impact of LVRS on the timing and selection of lung transplant candidates, Bavaria and coworkers[4] showed that 77% (24 of 31) of the patients with end-stage emphysema who underwent LVRS were removed from the transplant list due to a significant improvement in lung function 6 months after surgery. However, 4 of the 24 patients had more rapid declines in lung function and had to be relisted for lung transplantation. Perhaps more importantly, 23% of the patients in this case series (7 of 31 of patients) either showed no improvement, or in fact experienced a decline in lung function after LVRS. Three patients with α1 antitrypsin deficiency had unsatisfactory results following LVRS. There was one perioperative death. In contrast to the study at the University of Pittsburgh, 7 patients who completed only unilateral LVRS had a significant improvement in lung function after surgery. Based on this small number of patients, the authors suggested that LVRS may be used as a means to extend eventual lung transplantation in patients with end-stage lung disease secondary to emphysema.

Based on the current available studies, LVRS is a viable alternative to lung transplantation in selected patients with end-stage emphysema. Until new studies are available for review, patients with α1 antitrypsin deficiency, chronic hypercapnea, FEV_1 <20% of predicted together with a homogeneous emphysema pattern on CT scan or very low diffusion capacity should undergo lung transplantation instead of LVRS. Future studies need to further define selection criteria and the optimal surgical approach to LVRS in this group of patients.

8. Conclusions

In carefully selected patients with end-stage emphysema, LVRS offers symptomatic relief of breathlessness, improvement in lung function, exercise capacity, and quality of life. Thus, in patients who are both candidates for lung transplantation and LVRS, and who have a heterogeneous emphysema pattern on pre-operative evaluation, LVRS is reasonable alternative treatment or it can be used as a 'bridge' to lung transplantation. Lung transplantation is the preferred surgical modality in patients with FEV_1 <20% of predicted coupled with D_{LCO} of <20% or homogeneous emphysema. Similarly, patients with α1 antitrypsin deficiency will most likely have a better functional outcome with lung transplantation compared with LVRS.

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