Lung Transplantation and Lung Volume Reduction Surgery versus Transplantation in Chronic Obstructive Pulmonary Disease

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Lung transplantation and lung volume reduction surgery are surgical options for patients with advanced chronic obstructive pulmonary disease that is refractory to medical treatment. In this review, we discuss the differential indications for each procedure, as well as compare their risks and benefits. We also present an algorithm for selecting the most appropriate procedure for individual patients. Finally, we discuss the feasibility and role of lung transplantation after lung volume reduction surgery in the management of selected patients with chronic obstructive pulmonary disease.

Keywords: lung volume reduction surgery; lung transplantation; emphysema; advanced lung disease

Chronic obstructive pulmonary disease (COPD) is associated with significant morbidity and mortality. Despite optimal medical therapy, patients may have persistent dyspnea, decreased exercise tolerance, and a limited life span. For patients with COPD with severe emphysema, both lung volume reduction surgery (LVRS) and lung transplantation are potential treatment options.

It is imperative to assess the risks and benefits of each procedure before determining the treatment plan for an individual patient. Herein, we compare lung transplantation with LVRS with respect to indications and contraindications, and short- and long-term outcomes. We also examine the feasibility of performing lung transplantation after LVRS, and explore the role of sequential surgical procedures in patient management.

LUNG TRANSPLANTATION

The first human lung transplantation was performed in 1963, but it was not until 1986 that transplantation was performed in patients with COPD with any long-term success (1, 2). Advances in immunosuppressive therapy, graft preservation, and prophylaxis and treatment of infectious complications continue to improve outcomes. Even so, post-transplantation survival for patients with COPD is limited to 81.5% at 1 year, 64.0% at 3 years, and 49.0% at 5 years (3). The issue of the effect of lung transplantation on the survival of patients with COPD is still unclear, with European data indicating a survival advantage for transplant recipients, and no

such benefit seen in the U.S. population (4–6). However, since these investigations, several changes have taken place that allow for selection of patients with COPD with the poorest survival, which may impact survival advantage after lung transplantation. One of these is the introduction in May 2005 of the lung allocation system in the United States, which aims to prioritize patients who are most likely to die on the waiting list, with attention to optimizing overall survival benefit rather than the prior, less discriminating, listing system based on waiting time (7). Another factor is that we now have more information about the natural history of the disease with further identification of risk factors that would help select those patients with poorer disease-related survival who may benefit the most from transplantation (8). Lung transplantation can also offer other important benefits to patients with severe COPD such as improved exercise tolerance and quality of life (8).

However, the interplay of factors such as the limited supply of organs, variable waiting list times, and significant post-transplantation complications (e.g., opportunistic infections, acute and chronic rejection, and medication-related side effects) limits the utility of transplantation for patients with COPD to those who are most severely affected (3, 8). Even then, transplantation for COPD and α_1 -antitrypsin deficiency accounted for 60% of the almost 17,000 lung transplantations performed worldwide over the last decade (3).

PATIENT SELECTION FOR LUNG TRANSPLANTATION AND LVRS

Indications for Lung Transplantation

Lung transplantation should be considered for patients with severe COPD who remain symptomatic despite optimal medical therapy. Given the limited survival after lung transplantation, it is paramount to select candidates whose predicted disease-related survival is no greater than the predicted survival after transplantation (81.5, 64.0, and 49.0% at 1, 3, and 5 yr, respectively) (3). Although predicting survival for patients with COPD remains a challenge, several parameters may be helpful. The BODE (Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity) index developed by Celli and coworkers combines four factors known to be associated with increased mortality in COPD: body mass index, the degree of airflow obstruction (percent predicted FEV₁), dyspnea (modified Medical Research Council dyspnea scale), and exercise tolerance (six-minute-walk distance) (9). Patients with a BODE index score of 7–10 have a median survival of about 3 years and should be evaluated for transplantation, as should patients who are hospitalized with a COPD exacerbation complicated by hypercapnia (PaCO₂ $\geq$ 50 mm Hg), who have a 2-year survival of only 49% (9, 10). The National Emphysema Treatment Trial (NETT) showed that patients with emphysema with FEV₁ not exceeding 20% predicted and either homogeneous disease on high-resolution computed tomography scan (HRCT) or diffusion capacity (DL_{CO}) not exceeding 20% predicted have a median survival of about 3 years with medical therapy and are at high risk of death after LVRS with little chance of functional benefit; these patients should be considered for transplantation

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(11). Additional risk factors for reduced survival include pulmonary hypertension, hypoxemia, and hypercapnia, and multiple disease exacerbations; patients with these features are also potential candidates for lung transplantation, particularly if multiple factors coexist (12–16).

Indications for LVRS

Candidacy for LVRS is reviewed in detail elsewhere in this journal; but briefly, LVRS may be considered in patients with bilateral emphysema on HRCT scan and severe airflow obstruction with hyperinflation and air trapping on pulmonary function testing.

Factors Allowing Determination between LVRS and Lung Transplantation

Table 1 displays the factors favoring the choice of one procedure over the other.

Factors favoring LVRS over lung transplantation. The requirement for lung transplant recipients to undergo a relatively morbid surgical procedure followed by life-long immunosuppressive therapy may limit some patients from undergoing transplantation, but not LVRS (Table 1). Although advanced age has consistently been associated with higher mortality after transplantation, there is no absolute age cutoff beyond which transplantation is prohibited. However, patients aged 65 years or older must be thoroughly evaluated to identify any additional factors that may further increase the patient's transplantation-associated risk above a reasonable threshold (17, 18). LVRS may be an option for these patients, as the average age of LVRS-treated patients in the NETT was 66.5 ± 6.3 years and the relative effects of LVRS versus medical treatment did not vary with age (19). However, increasing age was a predictor of cardiovascular morbidity after LVRS, and thus it seems prudent to evaluate patient age along with other risk factors when determining suitability for LVRS (20). Lung transplantation is contraindicated in patients with chronic active infections such as hepatitis B, hepatitis C with histologic evidence of liver disease, and human immunodeficiency virus, because of the uncertain effects of immunosuppression post-transplantation on the activity of the chronic infection (18). Patients with lung cancer are not candidates for lung transplantation; LVRS, however, has been performed successfully in patients with limited-stage non-small cell lung cancer along with cancer resection. These combined procedures have allowed for a potentially curative resection in patients who may have been limited by poor lung function in the traditional approach, and should be considered in selected individuals (21–28). Other medical as well psychological and social factors may interfere with the patient's ability

to maintain the consistent immunosuppressive regimen and medical follow-up that are crucial after transplantation, but may not be barriers for LVRS.

Factors favoring lung transplantation over LVRS. The NETT studied patients with bilateral emphysema on HRCT and severe airflow obstruction as well as hyperinflation and air trapping on pulmonary function testing, and who met specific clinical and functional criteria (19). Patients who were not considered candidates for LVRS in the NETT, but who may be appropriate for lung transplantation, include those patients with severe COPD with predominantly small airway disease and a paucity of emphysema. In addition, patients with significant hypercapnia, hypoxemia, pulmonary hypertension, and six-minute-walk distance not greater than 140 meters may be of high surgical risk with LVRS but may be candidates for lung transplantation (19). Patients with emphysema with FEV₁ not greater than 20% predicted and either homogeneous disease on HRCT or DL_{CO} not greater than 20% have a median survival of about 3 years with continued medical treatment and should be considered for transplantation (11, 19).

OUTCOMES AFTER LUNG TRANSPLANTATION AND LVRS

Long-term Survival

Survival after lung transplantation at 1, 3, and 5 years, respectively, is 81.5, 64.0, and 49.0% for COPD and 77.4, 63.2, and 53.2% for α_1 -antitrypsin deficiency (3). This survival may be influenced by multiple factors including recipient age, procedure side (single vs. bilateral lung transplantation), recipient ventilator dependence, hospitalization, and long-term steroid therapy as well as transplantation center (3). In fact, long-term survival is greater in recipients 60 years of age or less if they received bilateral rather than single-lung transplantation. Thus, for younger patients receiving bilateral lung transplantation, the survival is 94.9, 84.7, and 68.2% in those less than 50 years of age, and 93.0, 79.7, and 60.5% for those between ages 50 and 60 years at 1, 2, and 3 years, respectively (29).

Survival after LVRS is better overall, approximating 90% at 1 year, 77% at 3 years, and 65% at 5 years (19). In this group, likewise, there is significant individual and subgroup variability, with relatively better surgical outcomes in patients with upper lobe-predominant disease. Because of several factors, including generally a greater degree of airflow obstruction in lung transplant recipients and the older average age of patients in LVRS series, the overall survival statistics are difficult to compare reliably. To further decipher this, Meyers and coworkers reported

TABLE 1. FACTORS ALLOWING DETERMINATION BETWEEN LUNG VOLUME REDUCTION SURGERY AND LUNG TRANSPLANTATION

Patient Factors Favoring LVRS over Lung Transplantation	Patient Factors Favoring Lung Transplantation over LVRS
<ul style="list-style-type: none"> • Age > 65 yr • Chronic medical conditions: <ul style="list-style-type: none"> • Chronic active viral hepatitis B, hepatitis C with biopsy-proven histologic evidence of liver disease, or HIV infection • Organ system dysfunction precluding appropriate immunosuppressive therapy: renal insufficiency, liver dysfunction, neuropathy, significant osteoporosis, uncontrolled diabetes • Refractory gastroesophageal reflux disease • Malignancy • Inability to maintain long-term follow-up • Psychiatric conditions limiting long-term compliance • Lack of social support 	<ul style="list-style-type: none"> • FEV₁ $\leq$ 20% predicted and either homogeneous disease or DL_{CO} $\leq$ 20% predicted • Lack of emphysema on HRCT • TLC < 100% predicted • RV < 150% predicted • PaCO₂ > 60 mm Hg • PaO₂ < 45 mm Hg • 6MWD $\leq$ 140 m, < 3 min unloaded pedaling on cycle ergometer • Pulmonary hypertension • Clinically significant bronchiectasis and/or recurrent pulmonary infections

Definition of abbreviations: 6MWD = distance walked in 6 minutes; DL_{CO} = diffusion capacity of carbon monoxide; HRCT = high-resolution computed tomography; LVRS = lung volume reduction surgery; RV = residual volume; TLC = total lung capacity.

99 patients who were candidates for immediate or eventual lung transplantation but who underwent LVRS. This group's mean FEV₁ was $24 \pm 8\%$ predicted, total lung capacity was $141 \pm 19\%$ predicted, residual volume was $294 \pm 54\%$ predicted, and diffusion capacity was $34 \pm 17\%$ predicted (30). Operative mortality was 4 of 99 (4%), and survival at 2 and 5 years was 92 and 75%, respectively. Although direct comparison with lung transplant recipients is limited given that not all of these patients were considered "immediate" candidates for transplantation and their physiologic parameters were not as severe as those reported in other lung transplant series, survival in this group far exceeded that after transplantation (31–33). Weinstein and coworkers compared patients with severe COPD who underwent LVRS with those who underwent transplantation (34). The patients undergoing transplantation had lower long-term survival as compared with patients undergoing LVRS, with a hazard ratio of 1.7 (34). Of note, at baseline, patients undergoing transplantation had more severe airflow obstruction (mean FEV₁ of 23.6 ± 8.5 vs. $31.9 \pm 17\%$ predicted), but no significant difference in age, body mass index, Borg dyspnea score, or six-minute-walk distance as compared with patients undergoing LVRS.

Short-term Mortality and Morbidity

Lung transplantation results in greater short-term mortality and morbidity and a longer postoperative course compared with LVRS. The transplantation procedure is generally of longer duration, with a more frequent requirement for cardiopulmonary bypass (31, 33, 35–37). For patients who receive single-lung transplantation (SLT), as well as those aged less than 60 years who receive bilateral lung transplant (BLT), the mortality is about 6% at 30 days and 9–15% at 90 days post-transplantation, compared with 2.2% at 30 days and 5.2% at 90 days post-LVRS in non-high-risk patients (high-risk patients are those with FEV₁ $\leq 20\%$ predicted and either homogeneous disease on HRCT or DL_{CO} $\leq 20\%$ predicted) (19, 28). Patients aged 60 years and older have even higher 30-day mortality (28).

Early (30-d) mortality after transplantation arises most often from graft failure (28.3%), noncytomegalovirus infections (20.3%), cardiovascular complications (10.8%), technical issues (8.2%), and acute rejection (4.7%) (3). Ninety-day mortality after LVRS in the NETT was related to a respiratory cause in 43% of patients, a cardiovascular cause in 18%, multisystem organ failure in 7%, cerebrovascular abnormalities in 4%, and was unclassified in 25% (20).

The same factors that limit short-term survival after transplantation can also lead to significant morbidity. In addition, diaphragm dysfunction and complications specific to SLT, such as native lung hyperinflation and native lung-related infections, may also lead to post-transplantation morbidity.

In the NETT, major pulmonary morbidity after LVRS occurred in 29.8% of patients, and included the need for reintubation (22%), pneumonia within 30 days (18%), mechanical ventilation for 3 or more days (14%), and the need for tracheotomy (8%) (20). Major cardiovascular morbidity occurred in 20.0% of patients and consisted of arrhythmias requiring treatment (19%), myocardial infarction (1%), and pulmonary embolus (0.8%) (20). The most common complication of LVRS in the NETT was air leak, which was present for a median duration of 7 days and required reoperation in 4.4% of cases (38). Postoperative in-hospital stay after LVRS is about 10 days compared with about 16–35 days after lung transplantation (31, 33, 38, 39).

Pulmonary Function and Gas Exchange

There is a dramatic improvement in pulmonary function and gas exchange after lung transplantation, reaching a maximum 6–9 months after transplantation (32, 33, 35, 36, 39, 40). The FEV₁

increases from 15–20% predicted to 80–90% predicted in BLT and to 50–60% predicted in SLT (32, 33, 39, 40). Hypoxemia and hypercapnia improve significantly and return to normal or near-normal values and almost all patients remain free of supplemental oxygen (32, 33, 40).

After LVRS, the improvement in FEV₁ is greatest at 6 months, but the increase is from about 28.1% predicted to 36.2% predicted (19). A study by Yusem and coworkers showed that the proportions of patients using supplemental oxygen at rest and with exercise fall significantly 6 months after LVRS (53 to 15% for use at rest and 95 to 46% for use on exercise) (41). Although patients with severe hypercapnia were excluded from most studies, patients with modest hypercapnia did show improvement to the normal or near-normal range (41, 42).

Respiratory Muscle Function

Patients have improved transdiaphragmatic pressures with maximal sniff after lung transplantation compared with similar patients with COPD not undergoing transplantation (43). On the other hand, diaphragm dysfunction occurs in about 3.2–42.8% of patients after transplantation, possibly because of phrenic nerve dysfunction (44, 45). Although this dysfunction may result in longer intensive care unit and hospital stays, it does not affect long-term outcome (45).

Diaphragm function after LVRS has been extensively studied; LVRS increases both diaphragm length and transdiaphragmatic pressures, and these improvements correlate with improvements in exercise capacity, dyspnea, and quality of life (46, 47). Both lung transplantation and LVRS improve lung elastic recoil and reduce ventilatory drive (48–50).

Exercise Capacity

Exercise capacity increases after transplantation, so that six-minute-walk distance doubles by 3–6 months after surgery, increasing from about 700–900 feet to about 1,300–1,700 feet (31, 33, 40). Maximum oxygen consumption also improves significantly, but remains limited to 40–60% of predicted normal values, likely related to abnormalities at the muscular level (51–55).

Exercise capacity also improves after LVRS, albeit much less so, with the six-minute-walk distance increasing from an average of 1,239 to 1,286 feet 6 months after surgery in the non-high-risk group in the NETT and the maximum work increasing from a mean of 40 to 45.5 watts (19).

Quality of Life

There are sustained improvements in multiple dimensions of quality of life after lung transplantation including physical functioning, role function, social function, mental health, and health perceptions; these improvements may diminish with the onset of late post-transplantation complications such as bronchiolitis obliterans syndrome (56–61). Transplant recipients did spend more time in the hospital and had more outpatient visits compared with patients undergoing LVRS (34). Importantly, 90% of patients were satisfied by their decision to undergo transplantation (60).

Patients undergoing LVRS also showed sustained improvements in general (Quality of Well-Being score) and health-related (St. George's Respiratory Questionnaire) quality of life, as well as improved nocturnal sleep quality and neurobehavioral functioning (19, 62–64).

Cost and Cost-effectiveness

The lifetime cost of care of a lung transplant recipient in the United States is approximately \$425,000 (65–68). The incremental cost-effectiveness ratio for transplant compared with waiting list patients (calculated as the difference in costs between the transplant recipients and waiting list patients divided by the

difference in quality-adjusted life years gained between the two groups) was \$176,817 in the United States (SLT or BLT) and \$48,241 for SLT recipients and \$32,803 for BLT recipients in the United Kingdom (65, 68).

The cost of LVRS totaled \$62,753 per person at 6 months after surgery and \$98,952 per person after 3 years (69). The incremental cost effectiveness ratio for LVRS compared with medical therapy was \$190,000 at 3 years but was projected to decrease to \$53,000 at 10 years (69). In the subgroup with upper lobe-predominant emphysema and low baseline exercise capacity, which showed the greatest overall benefits after LVRS, the cost per quality-adjusted life year gained was \$98,000 at 3 years and \$21,000 at 10 years (69).

Although direct cost comparisons may be limited because of differences in ascertainment and variable sources of data (single center vs. multicenter), surgical cost, total cost, and cost per quality-adjusted life year gained seem higher for lung transplantation than for LVRS, at least in the United States; comparison of costs for these two surgeries in other countries is even less certain (34, 69). In one retrospective study at a single center, during a mean follow-up of 2.4 ± 2.5 years after transplantation and 5.0 ± 3.1 years after LVRS, transplantation mean total costs were greater than LVRS costs (\$381,732 vs. \$140,637) (34). Regardless, both surgeries remain expensive compared with medical therapy, but may be cost-effective, particularly with selection of patients who incur the greatest benefits and maintain these benefits over time.

INDIVIDUAL DECISION MAKING: LVRS OR LUNG TRANSPLANTATION

When evaluating surgical options for a patient with severe emphysema, a thorough knowledge of the patient's medical history and physiology and goals and preferences is crucial to

the decision-making process. A suggested algorithm for the decision-making process is shown in Figure 1. In some patients, the decision will be straightforward, as they will have contraindications to either of the procedures (Table 1 and Figure 1). For instance, in order for a Medicare beneficiary to be a candidate for LVRS, the patient must essentially meet NETT inclusion criteria (Figure 1) (19). If not, providing that their disease is sufficiently severe, the patient may be evaluated for transplantation. In addition, patients with emphysema with an FEV₁ not exceeding 20% predicted and either homogeneous distribution of emphysema on HRCT or DL_{CO} not exceeding 20% predicted are at high risk of death after LVRS, and thus LVRS would not be an option for these patients (11). However, when treated with medical therapy, this group has a median survival of about 3 years; these patients should be evaluated for transplantation (19).

The differential risks and benefits of surgery compared with medical treatment in the subgroups identified by the NETT also assist in identifying the most appropriate procedure (Figure 1). First, patients meeting criteria for LVRS who have upper lobe-predominant emphysema and low exercise capacity have not only a benefit in exercise capacity and quality of life after LVRS; they have an improvement in mortality (19). Because no mortality benefit has been demonstrated in patients after transplantation, LVRS is the initial procedure of choice for these patients.

The predicted median survival of patients with upper lobe-predominant emphysema and high baseline exercise capacity is about 6 years for both LVRS and medically treated patients, and thus, unless other poor prognostic factors coexist, transplantation would not be indicated (62). LVRS can be offered to these patients with the objective of improving both exercise capacity and quality of life.

Patients with non-upper lobe-predominant emphysema and high baseline exercise capacity have a relatively good prognosis

Figure 1. Suggested algorithm defining surgical options for patients with severe chronic obstructive pulmonary disease. 6MWD = distance walked in 6 minutes; COPD = chronic obstructive pulmonary disease; DL_{CO} = diffusion capacity of carbon monoxide; HRCT = high-resolution computed tomography; PAM = mean pulmonary artery pressure; QOL = quality of life; RV = residual volume; TLC = total lung capacity. *BODE Index as developed by Celli and coworkers (see Reference 9).

with medical treatment, with about 20% mortality at 4 years, which is better than that after LVRS as well as transplantation. These patients should generally continue with medical therapy (19).

On the other hand, patients with non-upper lobe–predominant emphysema and low exercise capacity have poor survival after LVRS as well as after medical therapy (median survival, about 4 yr) (19). LVRS can be considered in these patients as it may improve quality of life; however, lung transplantation may be more desirable given its greater physiologic benefits.

Finally, it should be noted that although the available information about both LVRS and lung transplantation can help guide treatment, there is still tremendous individual variability that must be taken into account. Many patients with COPD will have significant comorbidities and overall debilitation that should be examined to assess the overall risk before proceeding with either surgical procedure.

LVRS FOLLOWED BY LUNG TRANSPLANTATION

Sequential procedures may be considered when LVRS results in no significant benefit or when LVRS leads to initial improvements followed by subsequent deterioration in a patient who is a transplantation candidate. To determine the feasibility of such sequential procedures, it is crucial to understand what impact, if any, the prior LVRS has on future lung transplantation. One single-center experience showed no difference in short-term morbidity, decline in lung function, or survival between transplant recipients who had undergone prior LVRS compared with those who had not (70). These findings were confirmed in an examination of the United Network for Organ Sharing (UNOS) database (71). LVRS was able to delay the time to transplantation by a median of 27 to 46 months (70, 71). With identification by the NETT of subgroups that derived the most benefits after LVRS, this bridge time may be even further lengthened (30, 70). By performing LVRS in groups of patients who are known to derive a benefit from this procedure with the option of transplantation in the future, sequential procedures may be employed to optimize overall patient outcome and survival. Such sequential procedures should be planned with the consideration that factors such as medical comorbidity or advancing age might preclude future transplantation.

CONCLUSIONS AND FUTURE DIRECTIONS

Both lung transplantation and LVRS are surgical options for select patients with advanced COPD. In some cases, the optimal procedure is clear but in others, the optimal choice may not be so clear. A thorough understanding of the indications, contraindications, risks, and benefits of each procedure, as well as the patient's goals and preferences, should guide the decision-making process. Sequential procedures, with LVRS followed by lung transplantation, may be feasible in select candidates.

Although LVRS and lung transplantation are established adjunctive therapies for patients with severe emphysema, their individual roles, and thus their relative roles, are still in flux. As LVRS is a relative newcomer, its popularity is likely to increase with further physician and patient familiarity with the procedure. In addition, nonsurgical, or bronchoscopic lung volume reduction, is currently under investigation and may prove beneficial (72). Avoiding an open surgical procedure may reduce overall complications and broaden the scope of potential candidates to include those with more severe disease, and those with non-upper lobe targets or cardiovascular issues that may prohibit an open thoracotomy but not the less invasive endobronchial approaches.

Transplantation in COPD, on the other hand, may become less common with the current lung allocation system based on

severity and using forced vital capacity as one of the main measures of severity (7). As forced vital capacity is particularly low in restrictive lung diseases such as idiopathic pulmonary fibrosis, these patients have shorter time on the transplantation wait list, resulting in longer wait list times for patients with COPD (73). LVRS, a procedure that generally offers less functional benefit but is significantly less morbid, can play a role in these individuals with the goal of offering some functional benefit, which could obviate the need for transplantation.

As prospective randomized comparisons of LVRS and transplantation are unlikely, single- and multicenter experiences will be helpful in further defining the respective roles of these two procedures.

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