Review Article

Transplant options for end stage chronic obstructive pulmonary disease in the context of multidisciplinary treatments

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Abstract: Lung transplantation (LTx) in advanced stage chronic obstructive pulmonary disease (COPD) patients is associated with significant improvement in lung function and exercise capacity. However, demonstration that the procedure also provides a survival benefit has been more elusive compared to other respiratory conditions. Identification of patients with increased risk of mortality is crucial: a low forced expiratory volume in 1 second (FEV_1) is perhaps the most common reason for referral to a lung transplant center, but in itself is insufficient to identify which COPD patients will benefit from LTx. Many variables have to be considered in the selection of candidates, time for listing, and choice of procedure: age, patient comorbidities, secondary pulmonary hypertension, the balance between individual and community benefit. This review will discuss patient selection, transplant listing, potential benefits and critical issues of bilateral (BLTx) and single lung (SLTx) procedure, donor-to-recipient organ size-matching; furthermore, it will describe LTx outcomes and its effects on recipient survival and quality of life.

Keywords: Lung transplantation (LTx); chronic obstructive pulmonary disease (COPD); referral; listing; BODE index

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Introduction

Chronic obstructive pulmonary disease (COPD) is now the fourth cause of death worldwide, and a leading indication for lung transplantation (LTx), representing almost one third of all procedures (1). The overall COPD prevalence ranges from 7% to 12% (2,3), and more than one thousand lung transplants are performed every year for severe COPD (ISHLT Transplant registry database). Due to the variability and slow development of the disease, selection of candidates, correct time for listing, as well as choice of procedure, remain under debate. Life expectancy of patients with GOLD stage III and IV disease is 6 years (4). After transplantation, due to chronic lung allograft dysfunction (CLAD), patients with COPD have a median survival of 5.6 years (1). The identification of patients at increased risk of mortality is crucial. In the early 90s, a study by Hosenpud on all patients listed for transplantation in the USA for emphysema, cystic fibrosis, or interstitial pulmonary fibrosis, failed to find a survival benefit in the emphysema group during 2 years of follow-up (5).

Referral and listing

The slow progression of COPD, compared to other respiratory disease, determined a lack of consensus among clinicians about timing for referral and listing patients for LTx. It is very important not to list a patient neither too early, because his post-transplant survival could be less than life expectancy due to the underlying disease, nor too late,

because of the risk of physical deconditioning, that can lead to a difficult weaning after transplant.

LTx should be considered for adults with chronic, end-stage lung disease who meet all the following general criteria:

- High (>50%) risk of death from lung disease within 2 years if lung transplantation is not performed.
- High (>80%) likelihood of surviving at least 90 days after lung transplantation.
- High (>80%) likelihood of 5-year post-transplant survival from a general medical perspective provided that there is adequate graft function (6).

Due to organ shortage and procedure-related mortality risk, it is important to consider absolute and relative contraindications to transplant. In 2006, a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation (ISHLT) indicated absolute contraindications to LTx (7); in 2014 the guidelines were updated, not including all possible clinical scenarios but rather highlighting common areas of concern (6).

The following are now considered as absolute contraindications:

- Malignancy in the last 2 years, with the exception of non-melanoma skin cancer; a 5-year disease-free interval is recommended, while there is still no agreement about the role of transplantation in patients with localized minimally invasive adenocarcinoma.
- Untreatable advanced dysfunction of another major organ system (e.g., heart, liver, kidney or brain) unless combined organ transplantation can be performed.
- Acute medical instability, including, but not limited to, acute sepsis, myocardial infarction, and liver failure.
- Chronic infection with highly virulent and/or resistant microbes that are poorly controlled pre-transplant.
- Evidence of active *Mycobacterium tuberculosis* infection.
- Class II or III obesity (BMI >35.0 kg/m^2).
- Uncorrectable bleeding diathesis.
- Significant chest wall/spinal deformity, expected to cause severe restriction after transplantation.
- Documented nonadherence or untreatable psychiatric or psychologic condition, associated with the inability to cooperate or comply with medical therapy.
- Absence of a consistent or reliable social support system.
- Substance addiction (e.g., alcohol, tobacco, or narcotics) that is either active or within the last 6 months.

Regarding active viral hepatitis B or C, or human immunodeficiency virus (HIV), the current opinion is that LTx can be considered in patients without cirrhosis or portal hypertension, if stable on appropriate therapy, or in patients with controlled disease with undetectable HIV-RNA, compliant on combined anti-retroviral therapy. In recent years, LTxs in carefully selected patients with controlled HIV infection have been reported (8), and some exceptions have been allowed among general contraindications, such as in case of chest wall deformity, although always considering a favourable risk/benefit ratio.

Once general contraindications have been excluded, the selection of candidates and the optimal time for transplantation is based on specific mortality risks: for the patients the target is to improve their quality of life, but for the clinicians the determinant of timing must be the prognosis.

Prior to the proposal of the BODE index, the degree of airflow obstruction measured by the forced expiratory volume in 1 second (FEV_1) was considered the most important predictor of mortality in COPD patients (9). In the 80's, patients with an FEV_1 <30% of predicted were considered to be adequate candidates for lung transplantation (10). In the following years, different studies have shown that the single measure of FEV_1 wasn't enough in order to predict mortality risk, so other factors were considered (11). Different studies focused on gas exchanges: while hypoxemia resulted a weak predictor of mortality, except in end-stage disease (12), hypo- or hypercapnia were associated with limited life expectancy (13). Hypocapnia can be a sign of respiratory muscle weakness due to increased ventilation; hypercapnia is strongly related to mortality, and is often nowadays used as a criterion for the selection of candidates. In countries, such as US and Germany, where priority in the waiting list is determined by a numeric value called the Lung Allocation Score (LAS), hypercapnia is used for the score calculation (14). Severe pulmonary hypertension (PH), with a median PAP >40 mmHg, was demonstrated to be strongly associated with limited survival in COPD patients in several studies (15,16): this factor must be considered in patient listing. Exercise capacity, measured through cardiopulmonary testing and the 6-minute walking test, was found to be closely associated with 5-year mortality (17,18), while the results regarding dyspnea assessment

though use of numeric scales were discordant in predicting prognosis, due to the subjective nature of the determinations (17,19). The National Emphysema Treatment Trial (NETT) studied 609 BPCO patients randomized to medical therapy: older age, supplemental oxygen use, lower hemoglobin, higher residual volume, lower CO diffusing capacity, lower maximal exercise capacity and lower lobe-predominant emphysema were identified as independent predictors of mortality. Surprisingly, FEV_1 was not found to have a significant association with mortality in the multivariate analysis, perhaps due to the fact that FEV_1 was severely reduced in the majority of patients and therefore reduced its power as a discriminating factor (20).

In 2004, in a study on 859 COPD outpatients, Celli validated a multidimensional grading system, called BODE index, based on four predictors of death:

- B: Body mass index (BMI);
- O: degree of airflow Obstruction;
- D: functional Dyspnea;
- E: Exercise capacity.

The quantification of the degree of pulmonary impairment and patient's perception of symptoms were included with two independent domains that expressed the systemic consequences of COPD. Every variable was associated with a point value, determining a weighted score ranging from 0 to 10. A BODE score of 7–10 was associated with an 80% mortality at 4 years, whereas a score of 5–6 conferred a 60% mortality at 4 years. This simple grading system appeared a better predictor of the risk of death from any cause and from respiratory causes than FEV_1 alone (21). In addition, the rate of decline of FEV_1 and frequent acute exacerbations of COPD, particularly those requiring hospitalizations, are recognized as good markers of disease progression and mortality (22,23): combining these information with the BODE index can help in managing patients (24).

In 2014, the ISHLT consensus update on recipient selection guidelines made specific recommendations regarding the timing of referral and of listing for Ltx in COPD patients (6):

- Referral: recommended for COPD patients with progressive disease despite maximal therapy, hypercapnia (>50 mmHg) or hypoxemia (<60 mmHg), or an FEV_1 <25% of predicted. Simultaneous referral of patients with COPD for both lung transplant and LVRS evaluation is appropriate. BODE index of 5 to 6 was suggested as a threshold for referral.
- Listing (presence of one criterion is sufficient):
  - BODE index score ≥7;
  - FEV_1 <15% to 20% of predicted;
  - Three or more severe exacerbations during the preceding year;
  - One severe exacerbation associated with acute hypercapnic respiratory failure;
  - Moderate to severe pulmonary hypertension.

It is important to underline that the LAS score doesn't actually include frequency of exacerbations, FEV_1, and degree of dyspnea: this brings to long waiting times for COPD patients in countries where the priority in the waiting list is determined by LAS (25). Conversely, in a recent retrospective analysis of survival, according to the BODE score, for patients with COPD in the United Network of Organ Sharing (UNOS) database of LTx candidates, Reed *et al.* found that candidates for LTx survive considerably longer than would be predicted by the BODE score: this is likely due to a lower prevalence of comorbid conditions, attributable to LTx evaluation screening process (26). These observations certainly support a reconsideration of the procedure.

Choice of procedure

While patients with bacterial colonization, such as in cystic fibrosis or bronchiectasis, must undergo bilateral LTx, patients with COPD can theoretically receive both single (SLTx) or bilateral (BLTx) transplant. The choice of the approach to perform is still debated, considering the potential benefits of BLTx and SLTx; however, no randomized or prospective controlled trials have evaluated these two procedures (27).

Despite the efforts to extend graft acceptability, LTx is still limited by donor pool shortage (28). In this context, the rational for SLTx is first of all maximizing the total number of patients transplanted, reducing the average waiting time and the mortality rate in the waiting list. In addition, total ischemia and operation time are shorter, the procedure is technically simpler, sternotomy is avoided, and early outcomes are satisfactory (29). In the 1970s, SLTx for COPD resulted in profound mismatches of ventilation and perfusion, because of high vascular resistance and high compliance of the native emphysematous lung; this lead to a greater ventilation to the native lung with increased perfusion to the allograft. The hypothesis was that COPD patients were poor candidates for SLTx (30). In the following years, as management of the allograft in the time after reperfusion improved, SLTx was found to be

a viable medium-term therapeutic option, and became the primary surgical technique for COPD patients (31). The main problems to face, regarding SLTx, are native lung hyperinflation, infection, and the risk of developing lung cancer.

In SLTx recipients, the compliance of the native emphysematous lung is higher than that of the allograft, so both acute and chronic native lung hyperinflation are possible; risk factors include pulmonary hypertension, severe airway obstruction, and significant air trapping prior to transplantation (32). The incidence of acute native lung hyperinflation is reported between 15 and 30%, and is rarely clinically severe (33), but in case of primary graft dysfunction (PGD), edema of the allograft can further increase hyperinflation, as well as in case of protracted positive pressure ventilation; patient management in these cases can be particularly demanding. The shift of the mediastinum can determine allograft compression and atelectasis; moreover, decreased venous return can lead to hemodynamic instability. While acute lung hyperinflation can be managed by ventilation strategies and early extubation, the chronic form can develop over years, leading to various possible complications, such as pulmonary artery thrombosis (34); in selected cases endoscopic or surgical native lung volume reduction is indicated (35,36).

The association of smoking with both COPD and lung cancer, as well as immunosuppression, determines a high risk of bronchogenic carcinoma in LTx recipients, particularly in the native lung after SLTx (37). Collins in 2002 reported a prevalence of lung cancer in the native lung of 2.5% of SLTx recipients, both for COPD and IPF, from seven US centers (38). In a review by Olland, the incidence after SLTx ranged from 0.4% to 8.9% of all cases, with an increase in more recent reports (39). The majority of patients present with advanced stage disease at the time of diagnosis, so a careful surveillance for changes in the native lung in all SLTx recipients is mandatory (37).

Other serious complications of the native lung are opportunistic infections and recurrent pneumothorax, with different impact on outcomes (40); surgical treatment can be necessary, and even pneumonectomy has been reported as rescue therapy (41).

In a context where guidelines are absent, in the last years BLTx has become the most performed procedure in COPD patients; over 57% of all COPD patients, reported to the ISHLT Registry between 1995 and 2015 underwent BLTx (1). This trend is related above all to the indication of longer survival rates of BLTx over SLTx, as discussed later; moreover, native lung complications are avoided.

However, it is currently improper to state that one procedure is absolutely superior to the other, particularly in patients aged 60 years or older. We believe that in the choice of the procedure, several factors have to be considered: age, patient comorbidities, secondary pulmonary hypertension, the balance between individual and community benefit. In absence of pulmonary hypertension, SLTx is a good choice for older patients with COPD, particularly if a significant difference in the perfusion of the native lungs is documented by pulmonary perfusion scans.

Surgical and anesthesiological considerations

Donor-to-recipient organ size-matching is a critical aspect of thoracic transplantation that also influences long term-survival (42). Due to lung hyperexpansion and consequently diaphragm adaptation, total lung capacity (TLC) in COPD patients is above that calculated based on height and sex. However, when evaluating a potential donor for a COPD patient, we have to consider that a lung volume similar to the size of the hyperinflated lung would produce inefficient respiratory mechanics, with negative outcomes. The lung size should be smaller than recipient TLC, in order to improve chest wall mechanics, similar to what is achieved with lung volume reduction surgery (LVRS) (43). For patients with emphysema, it is recommended that donor lungs present between 67% and 100% of the recipient's TLC (44); in case of SLTx, there is no clear consensus of evidence for recommended size-matching criteria. One study by Park reported optimal outcomes when the donor-recipient ratio was 0.89 (45). In case of larger donors, graft downsizing, by means of peripheral or anatomic resections, must be considered; reported results are comparable to standard procedures (46,47).

In several cases, COPD patients considered for lung transplantation have previously undergone bullectomy, LVRS or pleurodesis. This increases the risk of bleeding, particularly in case of cardio pulmonary bypass, but is not an absolute contraindication to LTx.

Hyperexpanded lungs can make pulmonary artery clamping problematic, before excluding lung ventilation. In these cases a degree of shunt is unavoidable, with a consequent drop in oxygen saturation. Nevertheless, the frailty of the lungs increases the risk of bleb rupture, bringing to problematic mechanical ventilation; this situation can occur even as a result of a barotrauma to the

emphysematous lung. COPD patients have a high risk of air trapping and dynamic hyperinflation during mechanical ventilation: this can lead to high intrinsic positive end-expiratory pressure (PEEP), with potential reduction of venous return to the right heart.

Differential lung ventilation is mandatory, both in DLTx and in SLTx. In COPD patients, a lung-protective ventilation, with reduced tidal volume, limited plateau pressure and low levels of PEEP, is necessary, in order to reduce ventilator-induced lung injury. At the end of the procedure, independent lung ventilation can minimize the impact of acute native lung hyperinflation, as well as intermittent disconnection of the endotracheal tube to allow native lung emptying. Prompt extubation, as soon as clinically possible, determines an improvement of the patient after LTx.

Survival after single and bilateral lung transplant

Lung transplantation in advanced stage COPD patients is associated with significant improvement in lung functions and exercise capacity (48-50). However, demonstration that the procedure also provides a survival benefit has been more elusive compared to other conditions such as idiopathic pulmonary fibrosis (51) and cystic fibrosis (52). Following lung transplantation, recent registry data report survival rates over 90% at 3 months, 79.9% at 1 year, and 55.7% at 5 years in COPD patients, with a median survival of 5.8 years (1). Compared to indications such as idiopathic pulmonary fibrosis, COPD patients have low short term post-transplant mortality due to a low risk of PGD (53,54). However, absence of an overall survival benefit for lung transplantation was found in an American and a Norwegian study analyzing a total of 1,406 COPD patients enlisted between 1990 and 2003 (5,55). Both studies found that post-transplant survival in COPD patients did not exceed waiting list mortality. Conversely, at least 4 studies conducted on a total of 9,441 COPD patients enlisted between 1984 and 2007 in the Eurotransplant region (56), the UK (57,58), the US (59), and Switzerland (60) found a positive survival benefit for lung transplantation. The Swiss study by Lahzami differs from all other studies in the field in that post-transplant survival was compared with mortality predicted by BODE score computation rather than with waiting list mortality (60). This approach potentially removes some biases derived from differences between transplanted patients and those on the waiting list. For the whole cohort, lung transplant offered a survival benefit, although this benefit was seen in the subgroup with a BODE score ≥7, but not in the subgroup with a BODE score <7. An individual survival benefit was observed in two thirds of the COPD transplant recipients. In the largest study to date on this issue, involving 8,182 COPD patients, Thabut *et al.* (59) estimated that 50.1% of patients undergoing single lung transplant and 63.7% of patients undergoing double lung transplant had a median survival with the transplant exceeding that without the transplant, indicating a survival benefit. The study also identified pre-transplant factors, such as FEV_1 below 16%, low BMI, age <60 years, and higher pulmonary artery pressure, that determine post-transplant survival. For example, 79% of patients with a FEV_1 below 16% of predicted at enlisting gained at least 1 year of survival post-transplant compared to only 11% among patients enlisted with an FEV_1 above 25% of predicted. The association between pre-transplant pulmonary hypertension and worse post-transplant survival has also been demonstrated in other studies (61,62).

Reasons that may determine the lack of a survival benefit among some studies may include short follow up, limited number of patients, time frame of the study dating back to the 1980's when lung transplantation was in its infancy, and premature listing for COPD patients in the early years, potentially reducing the advantage of transplant compared to staying on the waiting list (63).

Several studies (29,59,64-66) and international registry data (1) indicate that survival with double lung transplant may be superior to single lung transplant in COPD patients. Cassivi *et al.* (64) analysed 306 COPD/emphysema patients enlisted between 1988 and 2000 and found a significantly higher 5-year survival in patients undergoing bilateral lung transplantation (66.7%) compared to those undergoing single lung procedures (44.9%, P<0.005). Similarly, in an Australian study on 165 COPD patients enlisted between 1989 and 2003, 5-year survival was 81% for double lung transplant as opposed to 47% (P<0.01) for single lung transplantation (65). A criticism to these studies may be that confounding factors were not accounted for. For example, subjects receiving bilateral transplants are generally younger in age, and younger age has been associated with greater survival. Also, the year of transplantation is associated both with survival probability, and likelihood of receiving a single or double transplant. In the largest study analyzing international registry data on 9,883 COPD patients undergoing lung transplantation between 1987 and 2006, median survival time after double lung transplantation was significantly longer than that after single lung transplantation (6.41

vs. 4.59 years) (66). The beneficial effect of bilateral lung transplantation began approximately 1 year after the procedure, but is apparently lost in COPD patients transplanted over the age of 60. The study is noteworthy in that attempts to adjust for confounders were further addressed by using three different statistical methods: analysis of covariance, propensity-score risk adjustment, and propensity-score matching. The adjusted hazard ratio for bilateral lung transplant ranged from 0.83 to 0.89, depending on the statistical method. This translates into a 4.0% to 6.3% additional benefit in 5-year survival for double lung transplant compared to single lung transplant.

In the midst of a largely positive body of literature, one study failed to find a benefit of double lung versus single lung transplant in COPD patients after controlling for confounders with propensity score analysis (67). The study was carried out analysing US national registry data on lung transplants performed on 3,174 COPD patients between 2005 and 2012, after introduction of the lung allocation score. In the unadjusted analysis double lung transplantation was associated with a survival advantage compared to single lung transplantation (median survival 69.3 *vs.* 58.6 months, respectively, P=0.007 by log-rank test). However, after confounders were controlled for with propensity score analysis, differences in median survival were no longer apparent between bilateral and single lung transplantation (67.7 *vs.* 64.0 months, respectively; P=0.23 by stratified log-rank test).

Patients with emphysema associated with α1-antitrysin deficiency (A1ATD) likely present a different form of emphysema compared with patients who develop prevalently smoke-related COPD/emphysema. For example, A1ATD patients develop extensive emphysematous lesions earlier in life and generally gain access to lung transplantation at a younger age, a fact that may influence survival outcomes. Although A1ATD accounts for only approximately 2% of COPD cases (68), recent registry data indicate that end-stage lung disease due to A1ATD accounted for 5% of all lung transplants over the last 20 years (1). Tanash *et al.* (69) showed that lung transplant conferred a survival benefit to 83 A1ATD patients compared to 83 matched usual medical care A1ATD patients. The estimated median survival time was 11 years among transplanted patients, compared with 5 years for the non-transplant group (P=0.006). Similar results were obtained from a Danish national study involving 89 A1ATD patients transplanted between 1994 and 2010 (70). Data from a Swedish study indicate A1ATD patients had a longer median post-transplant survival compared to non-A1ATD emphysema patients (12 *vs.* 6 years, respectively, P=0.000) (71). COPD patients undergoing lung transplantation for non-A1ATD had a 70% higher mortality risk versus A1ATD patients. The authors found that 5- and 10-year post-transplant survival for A1ATD recipients were 75% and 59%, respectively, compared with 60% and 31% for COPD recipients without A1ATD.

Improvements in quality of life (QoL) following lung transplantation have been convincingly demonstrated in a number of small prospective studies involving patients with all indications for transplant, with COPD patients as a subset (72-76). Sustained QoL improvements following transplantation include better performance in physical activity, less restraint in social and leisure activities, more energy, and less pain compared to pre-transplant conditions. Nonetheless, post-transplant QoL remains below that attained in the normal population of healthy adults, likely as a result of medical co-morbidities, and immunosuppressant-related complications (74,77). Onset of chronic rejection has been associated with worsening quality of life following lung transplantation (78).

Health-related quality of life

Studies specifically addressing health-related quality of life (HRQoL) issues in post-transplant COPD patients are relatively scant. A Canadian study analysed HRQoL issues in 112 COPD patients, 66 of which underwent lung transplantation. Significant improvements in most HRQoL measures were found. A comparison of HRQoL results following single or double lung transplantation for different indications, suggests that notwithstanding lower FEV_1 recovery and increased risk of chronic rejection after the procedure, single lung transplant recipients had comparable long-term exercise tolerance and quality-of-life scores as patients who received double lung transplants (79).

Conclusions

A low FEV_1 is perhaps the most common reason for referral to a lung transplant center, but in itself is insufficient to identify which COPD patients will benefit from LTx; many variables have to be considered in the selection of candidates, time for listing, and choice of procedure. Positive survival benefit and significant improvements in HRQoL are demonstrated, if patients are accurately evaluated. There's a general agreement on better long term survival after BLTx, but in selected patients older than

60 years, SLTx is a good choice for patient's outcome, also reducing the mortality rate in the waiting list.

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Footnote

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