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Lung Transplantation for Chronic Obstructive Pulmonary Disease: past, present, and future directions

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Abstract

Purpose of Review—Lung transplantation offers an effective treatment modality for patients with end-stage chronic obstructive pulmonary disease (COPD). The exact determination of when to refer, list and offer transplant as well as the preferred transplant procedure type remains unclear. Additionally, there are special considerations specific to patients with COPD being considered for lung transplantation, including the implications of single lung transplantation on lung cancer risk, native lung hyperinflation, and overall survival.

Recent Findings—The International Society for Heart and Lung Transplantation most recent recommendations rely on an assessment of COPD severity based on BODE index. Despite the lack of evidence supporting a mortality benefit of bilateral over single lung transplantation for COPD patients, the majority of transplants performed in this population remain bilateral. Some of the concerns specific to single lung transplantation remain the possibility of *de novo* native lung cancer and the hemodynamic and physiologic implications of acute native lung hyperinflation.

Summary—COPD remains the most common worldwide indication for lung transplantation. Ongoing study is still required to assess the overall survival benefit of lung transplantation and assess the overall quality of life impact on the COPD patient population.

Keywords

Chronic obstructive Pulmonary Disease; Lung Transplantation; Native Lung Hyperinflation; Transplant Survival

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is one of the most important contributors to morbidity and mortality in the United States and remains the most common indication for lung transplantation worldwide (1). According to data from the International Society for Heart and Lung Transplantation (ISHLT) registry, there are more than one thousand lung transplants done every year for patients with severe COPD (2). Despite the advancements in

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management, the threshold for considering lung transplantation in patients with severe COPD, the timing for listing, the surgical modality and the use of single versus bilateral lung transplantation remains unclear. Since the trajectory of illness in patients with COPD is highly variable and some patients have a longer protracted course of illness and longer transplant wait list times, consideration of lung transplantation could put these patients at a particular disadvantage (3). Some practitioners also feel that utilization of the lung allocation scoring (LAS) in patient selection also puts these patients at a disadvantage compared to other chronic lung diseases (4). In this review article we aim to discuss indications, timing, and modality of lung transplant for COPD patients as well as discuss survival outcomes and some special considerations specific to the COPD population.

Lung Volume Reduction Surgery in the Potential COPD Transplant Candidate

As mentioned above the waiting time of patients with COPD are generally higher than other chronic lung diseases, including interstitial lung disease and cystic fibrosis (5). It remains unclear how to manage these patients and maintain their potential candidacy. Although lung volume reduction surgery (LVRS) has been associated with favorable outcomes in certain situations, given the more extreme fraction of expired volume in 1 second (FEV_1) cutoff recommendations for lung transplant compared to LVRS, only a small subset of potential LVRS candidates are also lung transplant candidates (6). In carefully selected patients, LVRS can delay the need for lung transplantation (7–9). Overall, though, the literature on the safety and impact of previous LVRS on future lung transplantation outcomes is underdeveloped. In 2014, Backhus et al. published their single center experience of lung transplant following previous LVRS. Over a 15 year period, 36 patients receiving LVRS plus transplant were compared with 138 patients receiving transplant alone. Operative and total hospital times were significantly longer in the combined group and post-transplant survival was significantly decreased compared to the transplant alone group. The total survival time, including time post-LVRS but prior to transplant, was similar in the combined (104 months) and transplant alone group (96 months) (10). Shigimura et al. in 2013 reported the outcomes of 25 LVRS plus transplant patients compared to 25 matched transplant alone subjects from a single center. While in-hospital mortality did not significantly differ between the two groups, previous LVRS patients had significantly higher rates of re-exploration for bleeding, renal injury requiring dialysis, and phrenic nerve injury as well as a diminished peak FEV_1 and six minute walk distance post-transplant (11).

While previous surgical LVRS does not adversely affect peri-operative transplant mortality, there is significantly added cost and patient morbidity as well as the need for two surgical procedures. The role of LVRS as a bridge to delayed lung transplantation deserves ongoing study.

There is even less published experience with endoscopic lung volume reduction prior to lung transplantation. Destors et al. published a case report of a patient with very severe emphysema receiving left-sided endoscopic placement of valves with resulting radiographic and spirometric improvements, but no symptomatic benefits. The patient subsequently

underwent a contralateral lung transplant with no reported complications (12). In a more recent matched case control study, there were no differences in peri-operative complications, length of stay, or one year mortality for COPD patients undergoing transplant after previous valve placement compared to those without valves. There were, though, higher rates of bacterial colonization, predominantly with stenotrophomonas (13). Given concerns for infection in immunocompromised transplant recipients, further research is needed to assess the impact of increased bacterial colonization rates as well as the overall safety of endoscopic lung reduction in potential transplant candidates.

Referral and Listing of COPD Patients for Lung Transplantation

In 2014, the ISHLT Pulmonary Council issued updated guidelines for referral and listing of patients with COPD (6). These guidelines suggest that patients with a BODE Index (incorporating body mass index (BMI), severity of airflow obstruction, level of dyspnea, and exercise capacity) of 5–6, progressive disease, significant hypercapnia and/or hypoxemia, and an FEV_1<25% predicted should be referred for evaluation for potential lung transplantation. Earlier referral of patients with advanced COPD to a lung transplant center not only allows the transplant team to assess patients for transplant candidacy but also provides patients and their families the opportunity to make fully informed decisions.

There is no consensus amongst pulmonologist in determining the exact timing for listing patients with COPD for lung transplantation. The pre- or post-bronchodilator FEV_1, hypoxemia, hypercapnia, low BMI, exercise capacity, low performance status on 6MWT and the subjective assessment of dyspnea have all been correlated to worsened outcomes in these patients but their utility in determining timing for referral is fairly limited (14–17). ISHLT consensus guidelines continue to use BODE index as a tool to guide timing of listing patients with COPD. Specifically the Society recommended the cut-off of a BODE score of 7–10 for listing these patients (6). This threshold is based on a study of 54 patients with COPD at two Swiss hospitals demonstrating improved median survival after transplant only in the subgroup with BODE>7 (18). Development of pulmonary hypertension (PH) heralds a poor prognosis and patients with moderate to severe PH patients are similarly recommended for active listing. In a study utilizing the United Network for Organ Sharing (UNOS) database, in a study of 1243 patients with COPD listed for lung transplantation, severe PH was associated with a hazard ratio for death of 7, highlighting the importance of monitoring pulmonary pressures in potential COPD transplant candidates (19). Patients with at least three severe COPD exacerbations in the previous year or an episode of acute hypercapnic respiratory failure are also at a significantly increased risk for death and are also recommended for active transplant listing (20, 21).

Single versus Bilateral Lung Transplantation in patients with COPD

In the 1970’s, early attempts at single lung transplant for COPD resulted in profound mismatches of ventilation (V) and perfusion (Q), leading to greater ventilation to the highly compliant emphysematous native lung with increased perfusion to the allograft (22). Impaired allograft compliance secondary to ischemia reperfusion injury further worsened the V/Q mismatch and was felt to make single lung transplant for COPD untenable. In the

proceeding decades, as management of the allograft in the time after reperfusion improved, single lung transplantation was found to be safe, the impact of V/Q mismatch was minimized, and single lung transplantation became the primary surgical technique for COPD patients (23). Over the last several decades, though, bilateral lung transplantation has gradually become the predominant surgical technique in this patient population, comprising over 57% of all COPD lung transplant procedures reported to the ISHLT registry between January 1995 and June 2015 (24).

Potential survival differences between bilateral and single lung transplants are one rationale for the switch to bilateral procedures. Older retrospective studies indicated a survival benefit of bilateral over single lung transplantation for COPD (25–27). These types of single center retrospective studies have the potential for significant selection bias, as treatment decisions are difficult to control for in statistical models. Thabut et al. demonstrated that while controlling for pre-transplant baseline characteristics, bilateral lung transplant provided a mortality benefit over single lung transplant for patients that were less than 60 years old (28). More recently, Schaffer et al. utilized propensity scores to control for potential selection bias in analyzing the UNOS thoracic registry of 3174 COPD patients undergoing lung transplantation from May 2005 through December 2012. There was no mortality difference at five years between single and bilateral transplant recipients, with single lung recipients surviving a median of 64 months and bilateral recipients 67.7 months (p=0.23) (4). Newer single center studies have found consonant findings; Bennett et al. demonstrated similar five year survival among patients receiving single lung transplant for COPD at the University of Colorado (53.2%) compared with bilateral COPD recipients from the nationwide UNOS registry (55.9%) (29). Markov models simulating single versus bilateral allocation strategies for COPD demonstrate increased waitlist mortality utilizing bilateral allocation and similar total post-transplant survival time compared to prioritizing single lung allocation. Additionally, single lung prioritization maximized the total number of patients transplanted (30). Given the societal impact of allocating limited resources, ongoing assessment of the risks and benefits of single versus bilateral lung transplant is needed. The optimal allocation strategy is likely dependent on age, patient level comorbidities (ex. pulmonary hypertension, nodules, etc.), regional location, and the prioritization of individual vs. societal benefit.

Acute Native Lung Hyperinflation

In COPD recipients of single lung transplants, the compliance of the native lung is high compared to the allograft, and can be further magnified by edema in the transplanted lung resulting from primary graft dysfunction in the setting of ischemia reperfusion injury. The differences in lung compliance can lead to acute native lung hyperinflation, especially in the setting of positive pressure ventilation. Symptomatic acute native lung hyperinflation is characterized by hemodynamic instability and cardiac output as a result of decreased venous return and contralateral shift of the mediastinum towards the allograft resulting in extrinisic allograft compression, atelectasis, hypoxemia, and hypercapnia. Studies demonstrate an incidence of acute native lung hyperinflation of 15–30% (31, 32). Techniques for minimizing the impact of acute native lung hyperinflation included independent lung ventilation with double-lumen endotracheal tubes, disconnecting the endotracheal tubes

intermittently to allow native lung empting and restore hemodynamic stability, early extubation, and ventilator manipulation, including reduced tidal volume and delivered breath frequency and increased inspiratory flow rates (31). Risk factors for native lung hyperinflation include PH, severe airways obstruction, and significant air trapping prior to transplantation. The potential deleterious impact of native lung hyperinflation, both acute and chronic, on transplant recipient post-transplant physiology provides rationale for bilateral lung transplant for selected COPD patients.

Lung Cancer after Lung Transplantation

Given the strong association of smoking with both COPD and lung cancer, COPD lung transplant recipients remain at high risk for bronchogenic carcinoma, predominantly after single lung transplantation. In a study of COPD recipients from 7 US transplant centers, 2% of patients developed subsequent lung cancer (33). In a retrospective review of lung transplant recipients in Leuven, Belgium, 9.8% of single lung transplant recipients (including patients with COPD and fibrotic lung disease) developed subsequent bronchogenic carcinoma while only 1.8% of bilateral recipients developed lung cancer (34). Lung transplant physicians need to be vigilant for monitoring for native lung bronchogenic carcinoma, especially among single lung transplant recipients. The increased cancer risk identified in single lung recipients is often utilized as rationale for bilateral transplantation in this patient population.

Survival Benefit to Lung Transplantation for COPD

Patients undergoing transplant for COPD have good short term survival, with an unadjusted three month mortality of 8–9% in the most recent ISHLT registry report (24). Much of this low short term mortality is due to the low risk of primary graft dysfunction resulting from ischemia reperfusion injury in the immediate post-transplant period (35, 36). The more controversial question is whether transplant provides an overall mortality benefit to COPD patients. The literature on survival benefit is mixed, with the ability to make definitive conclusions on survival benefits hindered by changes and differences in organ allocation algorithms (time based, lung allocation score, urgency, etc.) as well as the potential for long-term survival with extremely impaired quality of life for advanced COPD patients in the absence of transplant. For example, Stavek et al. demonstrated no mortality benefit to transplant in a Norwegian cohort when comparing patients waiting for transplant to those receiving lung transplants (37). Thabut et al. identified patient level factors that predicted improved overall survival with transplantation compared to no transplant for COPD, including FEV_1<16% predicted, lower BMI, younger age, and higher pulmonary arterial pressure (38).

The impact of risk factors leading to the development of COPD on overall transplant survival is also unclear. A recent single center study demonstrates significantly higher 5 and 10 year survival for patients with COPD secondary to alpha-1-antitrypsin deficiency (AATD) compared to COPD patients without AATD (HR 1.7, 95% confidence interval 1.02, 2.82) (39). A Swedish registry study similarly identified a survival benefit for lung transplant in patients with severe AATD (median survival 11 years vs. 5 years, p=0.006) (40).

The literature on the impact of lung transplant on quality of life for patients with COPD is limited. A single center study of 112 COPD patients demonstrates worsening quality of life with increasing BODE score. Importantly, patients with BODE 5–6 had similar improvements in quality of life to those with BODE 7–10, indicating that even patients not expected to have a mortality benefit with transplant should derive significant improvement in quality of life(41). In the absence of definitive survival benefits, the discussion of transplant benefit for patients with COPD should focus on the potential quality of life benefits associated with the procedure. In our experience, the vast majority of COPD patients garner significant improvements in their quality of life after transplant. What remains unclear is the trajectory of the improvement in the post-transplant period, specifically the expected length of time the average patient should expect to have improved quality of life.

Conclusion

Despite significant advances in the treatment of COPD over the last several years, lung transplantation remains the only option available for many patients with end stage COPD. Future research needs to focus on maximizing the ability of transplant to improve survival as well as quantifying the quality of life impact of lung transplant on COPD patient population.

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Key Points

- COPD remains the most common indication for lung transplantation worldwide and the second leading indication in the United States.
- The association between improved survival with lung transplantation for COPD remains unclear and requires further study.
- Single lung COPD lung transplant recipients are at an increased risk of acute native lung hyperinflation and native lung carcinoma.
- Ongoing study is needed to determine the ideal timing and type of transplant for patients with COPD and likely varies based on individual patient characteristics as well as local demographics and organ allocation practices.