Should Patients With Emphysema Be Offered Lung Transplantation?

Disclosures

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Lung transplantation evolved from heart-lung transplantation[1] and is performed as a single,[2,3] bilateral single,[4,5] or lobar transplant procedure.[6] Lung transplantation is considered an appropriate therapy for selected individuals with end-stage lung disease that is unresponsive to medical therapy and that results in progressive clinical deterioration. A recent publication endorsed by the International Society for Heart and Lung Transplantation (ISHLT), the American Thoracic Society, the European Respiratory Society, and the American Society of Transplantation produced international consensus guidelines on patient selection and evaluation for these procedures.[7] According to these guidelines, lung transplantation is a therapeutic option for patients with end-stage lung disease that falls into 1 of 4 main categories: pulmonary vascular disease, restrictive pulmonary disease, obstructive airway disease, or suppurative disease.

Pulmonary vascular diseases include primary pulmonary hypertension, pulmonary hypertension secondary to systemic disease, and Eisenmenger's syndrome. Restrictive pulmonary diseases include idiopathic pulmonary fibrosis, fibrosis secondary to connective tissue disease, sarcoidosis, and chronic allergic alveolitis. Obstructive diseases include emphysema with or without alpha-1-antitrypsin deficiency, Langerhans cell granulomatosis, and lymphangioleiomyomatosis. Suppurative diseases include cystic fibrosis and bronchiectasis.

Is it appropriate to consider lung transplantation in a patient whose condition has deteriorated despite optimal medical therapy to the point that the patient's functional status is poor, the New York Heart Association is < Class 3, and the estimated life expectancy is limited to 1-2 years?

The timing of referral for consideration of lung transplantation is not based on any single factor, but rather on a constellation of symptoms, physical findings, and laboratory findings. Knowledge of the
natural history of each of the diseases amenable to transplantation assists lung transplant clinicians in determining the appropriate timing for referral and acceptance onto a waiting list. The major barrier to widespread application of lung transplantation is the ever-increasing disparity in the number of patients who would potentially benefit from lung transplantation and the number of cadaveric donor lungs available. This situation is a global problem and appears to be worsening.

Consequently, the question of whether patients in certain disease groups, particularly those with chronic obstructive pulmonary disease (COPD), should be candidates for lung transplantation has arisen. The ISHLT 22nd Annual Meeting and Scientific Sessions in Washington, DC,[8] closed with a debate on this topic led by Dr. Ramona Doyle from Stanford, California and Dr. Keith McNeil from Brisbane, Australia.

This debate was spawned by a publication by Hosenpud and colleagues[9] that reported findings of an analysis of data from the joint United Network for Organ Sharing/ISHLT Thoracic Registry. The aim of this study was to clarify the actual survival benefit of lung transplantation in patients with cystic fibrosis, idiopathic pulmonary fibrosis, and emphysema. Using a time-dependent, nonproportional hazard analysis,[10] the risk of mortality after transplantation was compared with the risk of mortality in patients on the transplant waiting list. This analysis assumed there was a constant death rate on the waiting list, which has been demonstrated in patients on renal dialysis awaiting cadaveric renal transplantation.[11] However, since no peer-reviewed data on waiting list mortality is available for patients awaiting lung transplantation, this model may not be valid.

The data suggested a survival benefit following lung transplantation for patients with cystic fibrosis and idiopathic pulmonary fibrosis.[10] By contrast, the mortality rate on the waiting list in patients with emphysema was low and posttransplant survival did not exceed waiting list survival during the 2-year follow-up period. These findings should be interpreted with caution for several reasons. First, because the data were derived from many centers prior to publication of international guidelines, the participating centers were unlikely to have a uniform policy for listing patients for transplantation. Moreover, given the long waiting list time for lung transplant candidates, some centers list patients at early stages in the development of severe lung dysfunction.[12,13] This practice clearly creates a bias toward waiting list survival. The data reflect outcomes only from centers in the United States where waiting time is an important determinant of organ allocation, which encourages larger transplant centers to list patients early. In fairness, however, the Dutch lung transplant group[14] published data that demonstrated no difference in survival in patients with emphysema who were transplanted compared with those remaining on the waiting list, although this study was underpowered to derive a clear conclusion. A second concern is that “group” data should not be interpreted to mean that no patient with emphysema will benefit in terms of survival following lung transplantation. On the contrary, it is clear that patients with emphysema who are hypoxemic, hypercapneic, underweight with pulmonary hypertension, and have a history of previous intubation for an episode of severe type 2 respiratory failure complicating an exacerbation have a very different prognosis from that of disabled, stable patients.

**Guidelines for Referral of Patients With COPD for Transplant Evaluation**

It is important that every effort is made to exclude asthma and maximally treat any reversible component of the airway disease prior to referral for transplant evaluation. Pulmonary rehabilitation and long-term oxygen therapy, when appropriate, should also be included as part of overall medical
management prior to referral to a transplant center. Other treatment options, such as lung volume 
reduction surgery (LVRS) for emphysemic patients, may also be considered in appropriate 
candidates.\cite{15,16} Patients with COPD are considered to be potential candidates for transplantation if 
they meet the following criteria: FEV$_1$ < 25% of predicted value after bronchodilator therapy and/or 
PaCO$_2$ > 55 mm Hg (7.3 kPa) and/or elevated pulmonary artery pressures with progressive cor 
pulmonale. Preference should be given to hypercapneic patients with progressive deterioration who 
require long-term oxygen therapy, as these patients have the poorest prognosis.\cite{17}

**Other Surgical Treatment Options**

Lung transplantation remains an appropriate consideration for some individuals with emphysema -- 
those with end-stage disease and progressive deterioration in quality of life and exercise tolerance. 
However, LVRS has been proposed as an alternative treatment option in carefully selected patients 
with severe diffuse emphysema. Optimal patient selection criteria for treatment of emphysema by 
LVRS were clarified by the results of the National Emphysema Treatment trial, a randomized, 
multicenter clinical trial that compared LVRS with medical treatment.

The National Emphysema Treatment trial research group emphasized that the subgroup of patients 
with emphysema who should be considered for LVRS are different from the subgroup of patients 
who should be considered for transplantation.\cite{18} Patients considered for LVRS should have ceased 
tobacco use and be markedly disabled despite completing a comprehensive pulmonary 
rehabilitation program. They should have marked air-flow obstruction, but with an FEV$_1$ > 0.6 L in 
absolute volume with marked thoracic hyperinflation, and their lungs should show sufficient 
heterogeneity in the distribution of emphysema to provide the surgeon with target areas of 
nonfunctioning, volume-occupying lung that is amenable to surgical resection. Patients with alpha-
1-antitrypsin deficiency are not suitable, nor are those with pulmonary arterial hypertension. The 
research group cautioned against the use of LVRS in patients with emphysema who have a low 
FEV$_1$ and either homogeneous emphysema or a very low carbon monoxide diffusing capacity. 
These patients were found to be at high risk for death after LVRS and unlikely to benefit from this 
approach. Furthermore, LVRS and lung transplantation should not be considered mutually 
exclusive procedures, as there is now clear evidence that patients can undergo successful lung 
transplantation following LVRS.

**Choice of Operation**

A related debate is the over the surgical approach: unilateral vs bilateral. There are several reasons 
why unilateral lung transplantation is an attractive option in patients with emphysema. The 
procedure is technically straightforward, and most recipients do not have pleural adhesions. 
Furthermore, the functional results of single lung transplantation are acceptable; most patients 
achieve an FEV$_1$ of 50% of predicted value. Although these improvements are not as dramatic as 
those achieved following bilateral lung transplantation\cite{19} there are no major differences in 
maximum exercise performance, and in general, a significant degree of limitation persists with 
maximum oxygen consumption ranging between 45% and 52% of predicted value reported for both 
procedures. Patients who remain free of obliterative bronchiolitis (OB) do, however, enjoy a normal 
lifestyle and good quality of life.\cite{20} The obvious advantage of single lung transplantation is that this 
procedure enables more transplantation procedures to be performed if both donor lungs are
acceptable.

On the other side of the debate, critics of single lung transplantation are concerned about hyperinflation of the native lung and the potential for compression of the contralateral graft. Although LVRS on the opposite side can be considered, the use of single lung transplantation may be best limited to patients without bullous disease and older patients of smaller stature who may be less able to tolerate the more demanding bilateral procedure. In favor of bilateral lung transplantation, there is evidence that long-term survival is slightly better compared with unilateral transplantation. Therefore, bilateral lung transplantation is the preferred procedure for patients who are younger and of larger stature.

OB

The long-term outcome of patients with COPD undergoing single or bilateral lung transplantation is limited by the development of OB, defined by progressive airflow obstruction and deterioration of graft function. OB is characterized histologically by inflammation and fibrosis of the small airways. The current 5-year survival of 50% to 60% following lung transplantation is significantly lower than the survival rates for other types of solid organ transplantation, primarily because of the development of OB. In addition, sepsis accounts for up to 30% of late deaths and may occur in the presence of OB (patients with OB may in fact be predisposed to sepsis).

Conclusions

The article by Hosenpud and colleagues and its message for both potential transplant candidates with COPD and their caregivers is thought provoking. It must be emphasized that this analysis assessed only duration of survival; it did not include quality of life. Several studies have shown substantial improvement in indices of health and quality of life in patients undergoing lung transplantation, including those with a preoperative diagnosis of emphysema. The decision of whether to offer lung transplantation to a patient with emphysema is, therefore, complex and must take into account not only the duration of expected survival, but also quality of life. Severely disabled patients who do not have features suggestive of life-threatening disease should be made aware that their survival may not be prolonged by transplantation. However, the vast majority of these patients wish to be placed on the transplant waiting list. It is an interesting observation that the principal gain from transplantation for patients with emphysema is quality of life and the best outcome for this group of patients is achieved with the worst economy of donor organs, namely, bilateral lung transplantation. Therefore, the onus of responsibility regarding suitability of patients for transplantation is on the evaluation committee. It is reassuring that patients with idiopathic pulmonary fibrosis and cystic fibrosis derive improvements in both quantity and quality of life following appropriate transplantation.

While the results of the study by Hosenpud and colleagues suggest that lung transplantation for patients with emphysema is difficult to justify on the grounds of survival outcomes alone, clearly, there are individual patients with emphysema who experience survival advantages from lung transplantation. Moreover, the findings from this study were exclusively based on data from the United States, where waiting time is an important determinant of organ allocation. This policy supports the listing of patients at an early stage and may not accurately reflect practice regarding listing outside of the United States. The publication of international guidelines for the selection of
lung transplant candidates is timely and should serve as a useful aid to transplant physicians and surgeons in listing candidates for lung transplantation at an appropriate time.

References