Listing the Patient: Deciding When Transplantation Is the Only Viable Life-Sustaining Option

Jonathan B. Orens, MD
Associate Professor of Medicine,
Division of Pulmonary and Critical Care Medicine
The Johns Hopkins School of Medicine
Medical Director, Lung Transplantation Program
Johns Hopkins Hospital
Baltimore, Maryland

Transplantation of the lungs became an acceptable therapeutic option for patients with end-stage lung and pulmonary vascular disease in 1981, following the first successful human heart-lung transplantation performed for a patient with primary pulmonary hypertension.[1,2] At the time no other efficacious therapy was available and the transplantation was performed as an experimental "last ditch" life-saving procedure. Since then, both single and double lung transplantation has become part of the routine armamentarium to treat patients with pulmonary arterial hypertension (PAH) when all other measures fail. For highly selected patients, lung transplantation offers the possibility of improved survival and functional status.[1,3-5]

However, despite major strides in the field of lung transplantation, numerous shortcomings are still associated with this procedure, including lack of available donor lungs, need for lifelong immunosuppression, acute and chronic allograft rejection, infection, and extremely high costs of the procedure and post-transplantation care. Furthermore, since the time of that first heart-lung transplantation, treatment options for patients with PAH have changed dramatically. Both calcium channel blockers and intravenous epoprostenol have shown proven benefit and in many cases provide adequate treatment to prevent or prolong the need for transplantation.[6-12] Recently agents such as endothelin antagonists and sildenafil have been added to the medication armamentarium, further broadening therapeutic options. Indeed, lung transplantation has moved from a primary treatment for pulmonary hypertension to a therapy that complements the current medical options to prolong life and improve quality of life.

Candidate Selection for Transplantation

Appropriate candidates for lung transplantation have end-stage lung disease without concomitant illness that would adversely affect their survival following transplantation. In selecting candidates for this procedure it is important to consider the severity of the patient's illness as it relates to projected survival without transplantation, coexisting medical problems, and the financial cost of the procedure. Although assessing projected survival without transplantation is difficult, it is extremely important with regard to selecting the appropriate timing for lung transplantation, since waiting periods for lung transplants now average 1.5 to 2 years. Although there are ongoing efforts to change the strategy for donor lung allocation, currently in the United States the priority for obtaining a lung transplant is based solely on the time accrued on the waiting list, after matching for ABO blood type and body size. This is unlike that for other solid organ transplants, where consideration is given to the severity of the recipient's disease. Therefore, in order to select the appropriate time to list patients for this procedure, one must carefully consider the candidate's projected survival against the waiting period for transplantation.

Table 1—Indications for Lung Transplantation in Pulmonary Arterial Hypertension.

New York Heart Association functional class III or IV
Mean right atrial pressure ≥10 mm Hg
Mean pulmonary arterial pressure ≥50 mm Hg
Cardiac index ≤2.0 L/min/m^2
Failure of medical therapy in the setting of:
WHO class III or IV symptoms
Mean right atrial pressure ≥10 mm Hg
Mean pulmonary arterial pressure ≥50 mm Hg
Cardiac index ≤ 2.0 L/min/m^2

WHO = World Health Organization

In order to assure some consistency across transplant centers, international guidelines have been published that are used by many centers to select lung transplant candidates.[13] These criteria are also used by most insurance carriers for coverage purposes. Although these guidelines were proposed to develop standards across centers, individual programs continue to use their own selection criteria, which vary from center to center. Thus, a candidate who is unacceptable at one program may be considered acceptable elsewhere. The guidelines for patients with primary pulmonary hypertension are outlined in **Table 1**.

There are both absolute and relative contraindications to transplantation (**Table 2**). It is important to note that the criteria used for inclusion and exclusion are general guidelines to help select potential candidates. In special circumstances, individual patients may be accepted for transplantation even if they do not meet all of the criteria in these guidelines.

Timing of Lung Transplantation

Although many patients may improve or remain stable with medical therapy for several years, at some point this therapy may fail, requiring lung transplantation as the only life-sustaining option.

Table 2—Contraindications to Lung Transplantation

Relative contraindications

Age:

- >65 for single lung transplantation
- >60 for bilateral single lung transplantation
- >55 for heart and lung transplantation

Psychosocial instability

Mechanical ventilation

Chest wall deformity

Asymptomatic osteoporosis

History of substance abuse

Weight outside of acceptable range (morbid obesity or severely malnourished)

Prednisone use >20 mg/day or 40 mg every other day

Bilateral pleurodesis (for cardiopulmonary bypass candidates)

Absolute contraindications

HIV infection

Bone marrow failure

Cirrhosis of liver or active hepatitis B or C infection

Chronic renal failure (creatinine clearance <50 mL/min)

Malignancy precluding long-term survival

Other life-limiting conditions

Active tobacco smoking or other substance abuse

Significant coronary artery or peripheral vascular disease

Impaired left heart function unless considered for heart-lung transplant

Severe symptomatic osteoporosis

Sputum growing antibiotic panresistant bacteria

Because of the long waiting periods for lung transplantation in the United States, and the unpredictable response to medical therapy, deciding when to refer these patients for transplant remains a clinical conundrum. Patients who remain stable or improve with medical therapy should not be prematurely exposed to the risks of surgery and long-term immunosuppression. However, some patients may be observed during medical therapy too long, ultimately being referred for transplantation too late to survive the waiting period for a transplant. Additionally, some patients may be referred late enough in their course to have developed additional problems, such as malnutrition and renal insufficiency, placing them at higher risk for surgery.

Carefully monitoring the response to medical therapy at regular intervals is crucial to assess whether the treatment remains effective. For those in whom all forms of medical therapy fail, transplantation should be offered before the patient becomes too ill to enjoy a successful outcome. Lung transplantation should be considered for patients with PAH in whom therapy with vasodilators fails. Because of the long waiting period for lung transplantation, and the unpredictable rate of decline for some patients, many centers advocate listing patients for transplantation as soon as the diagnosis of PAH is established, while others recommend that listing should occur when and if there is failure of medical therapy (ie, vasodilators and anticoagulation). Accordingly, the overall clinical picture must be assessed for each patient in order to allow ample waiting time for this potential life-saving therapy. Thus it is left to the treating physician and transplant specialist to make some predictions regarding an individual patient's survival with medical therapy.

Resting hemodynamics, 6-minute walk or shuttle test results, and functional class (eg, World Health Organization) status have each been demonstrated to predict survival in PAH.[14-17] Anticoagulation with warfarin, calcium channel blockers, and long-term epoprostenol have each been documented to improve survival in PAH,[8,18-20] and response to these therapies must be considered in relation to the timing of transplantation. Since the prognosis for patients with PAH may change continuously in response to treatment, pretreatment survival predictions using baseline static measurements, such as functional class, are of little value in determining the need for transplantation. Initiation of epoprostenol may dramatically improve symptoms and prognosis, potentially postponing or obviating the need for lung transplantation.[10] Indeed, vasodilator responders with PAH have a 90% to 95% 5-year survival when initiated on oral calcium channel blocker therapy and therefore are generally not initially listed for lung transplantation.[8] Unfortunately, the vast majority of patients with PAH (75% to 85 %) are nonresponders, and without therapy face a 5-year survival of less than 40%. It is this latter group that should be considered for continuous intravenous epoprostenol therapy and listing for lung transplantation. Aalthough long-term data with epoprostenol are limited, improved 5-year, or 50 month (50% to 60%) survival, has been reported.[19,20]

Thus, the potential effect of epoprostenol on survival must be considered when evaluating patients for lung transplantation. At our center, we generally begin the evaluation process for lung transplantation when WHO class III symptoms develop. If there are no significant contraindications for transplantation, these patients are listed and symptoms are monitored while time is accrued on the waiting list. If symptoms stabilize during medical therapy, these patients are removed from the active list; reactivation occurs if medical therapy begins to fail.

Effect of Epoprostenol on Timing of Lung Transplantation for PAH

Improvement in symptoms and survival with continuous infusion epoprostenol has had a significant impact on the timing of lung transplantation.[10,11,21] Treatment with this therapy may result in three potential clinical responses. (1) A few patients experience no significant improvement, and in this group medical therapy is considered to have failed. In these individuals, transplantation is the only viable life-sustaining option. These patients are usually maintained on epoprostenol in the hope that their disease will stabilize until transplantation. (2) Another potential response, and fortunately the most likely (occurring in >90% of patients), is improvement with

epoprostenol with a demonstrable reduction of at least one point in WHO symptom class within the first 3 to 6 months. However, some patients develop a recurrence of symptoms despite further increases in their epoprostenol dose and require further consideration for transplantation. These patients will have benefited from epoprostenol in the short term by deferring the immediate need for lung transplantation.[10] (3) Some patients develop a substantial and long-lasting (years) benefit from epoprostenol, and lung transplantation will be deferred indefinitely.

Deciding where an individual patient lies within these three groups at an isolated point in time can be a challenge clinically. Serial assessment of functional status together with direct measurement of hemodynamics allows one to best determine the response to therapy. For those who are good long-term responders to epoprostenol, it remains unclear how long the benefit may hold, as the longest survival time of a patient receiving epoprostenol is now well over 10 years. However, it is important to remember that if one waits too long, until functional status markedly declines and hemodynamics begin to fail, the patient may become too sick for a successful transplant.

Type of Transplant

The operation of choice for primary pulmonary hypertension remains controversial. Combined heart-lung transplantation,[22] single lung transplantation[23-25] and double lung transplantation[10,23] have all been performed successfully. However, combined heart-lung transplantation is rarely necessary for PAH, since the right ventricle tends to recover function relatively quickly following either single or double lung transplantation.[25] Given the success of single and double lung transplantation, coupled with the limited supply of heart-lung donor blocks, single and double lung transplantation has almost completely replaced heart-lung transplantation for PAH in the United States.

Whether one should offer single or double lung transplantation for PAH is not clear, as there are pros and cons for each approach. Single lung transplantation is a less invasive and shorter surgical procedure, allows two recipients to be served from a single donor, and the waiting periods are shorter than for double lung transplants. However, the most recent International Society for Heart and Lung Transplantation (ISHLT) registry data show a slight long-term survival advantage for patients with double lung transplants (all diseases combined) compared to single lung transplants, although the difference is not statistically significant for patients with PAH.[26] There is, however, one important potential problem with single lung transplants for pulmonary hypertension that has influenced many programs to favor double lung transplantation. With single lung transplantation, blood preferentially flows in the pulmonary circuit toward the new lung; little flow goes to the native lung because of the severe pulmonary vascular disease. If the new lung develops infection or rejection, a severe shunt can develop, causing profound hypoxemia and making management extremely difficult.[27]

Immunosuppression

Following lung transplantation, recipients must receive lifelong immunosuppression to prevent allograft rejection. Unfortunately, numerous side effects are associated with these medications. The major consequence of long-term immunosuppression is an increased rate of infection. Following transplantation there is an increased risk for bacterial, viral (particularly cytomegalovirus), and fungal infections.[28,29] The risk of infection relates inversely to the time from the transplant procedure.[28,29] This is due in part to both mechanical factors and the intensity of immunosuppression.[28,30] Although the risk of infection decreases as the amount of immunosuppression is reduced over time, the risk never returns to that of normal individuals.

Other risks of immunosuppression relate specifically to each drug. Most centers use a triple-drug-based regimen including cyclosporine (Neoral) or tacrolimus (Prograf), with azathioprine (Imuran) or mycophenolate mophetil (CellCept) and prednisone. Both cyclosporine and tacrolimus may induce hypertension and nephrotoxicity, while azathioprine and mycophenolate produce leukopenia. Long-term corticosteroid use is associated with a litany of problems, including osteoporosis, skin bruising, hyperglycemia, cataracts, and myopathy. In addition to these problems, long-term immunosuppression is associated with an increased risk of cancer, particularly post-transplant lymphoproliferative disorder, which has been reported at a rate of around 6% following thoracic organ transplantations.[31]

Lung Transplantation Outcomes

Survival

The success of lung transplantation can be measured according to several criteria, including survival, physiologic function, quality of life, and cost benefit. According to 2003 US Scientific Registry data, overall survival following lung transplantation is currently 77.4% at 1 year and 42.5% at 5 years.[32] Lung transplant recipients with PAH do not fare as well, however, having a 1-year survival of 72%, with much of this mortality due to perioperative deaths.[32] The 5-year survival is 37%.[32] **Figure 1** shows survival outcome by disease in patients from the United Network for Organ Sharing (UNOS)/ISHLT registry (data analysis through 2001).

A number of factors are responsible for early mortality (0 to 30 days). These include infection (23.5%), primary graft failure (30.5%), cardiovascular factors (11.5%), acute rejection (4.9%), bronchiolitis (0.5%), technical factors (8.3%), and other causes (20.5%).[33] The factors responsible for late mortality differ from those for early mortality. Over the long term, chronic allograft rejection, manifested pathologically as obliterative bronchiolitis, is the single most important factor limiting the overall success of lung transplantation. Obliterative bronchiolitis occurs in at least 40% of patients by 2 years and in up to 70% by 5 years,[34] and it is the cause of death in 50% of those affected. Other causes of late mortality include infection, malignancy, and other comorbidities. Prior to the development of epoprostenol, transplantation provided a survival advantage for patients with PAH when comparing transplant survival with

(article continues in pull-out) ▶

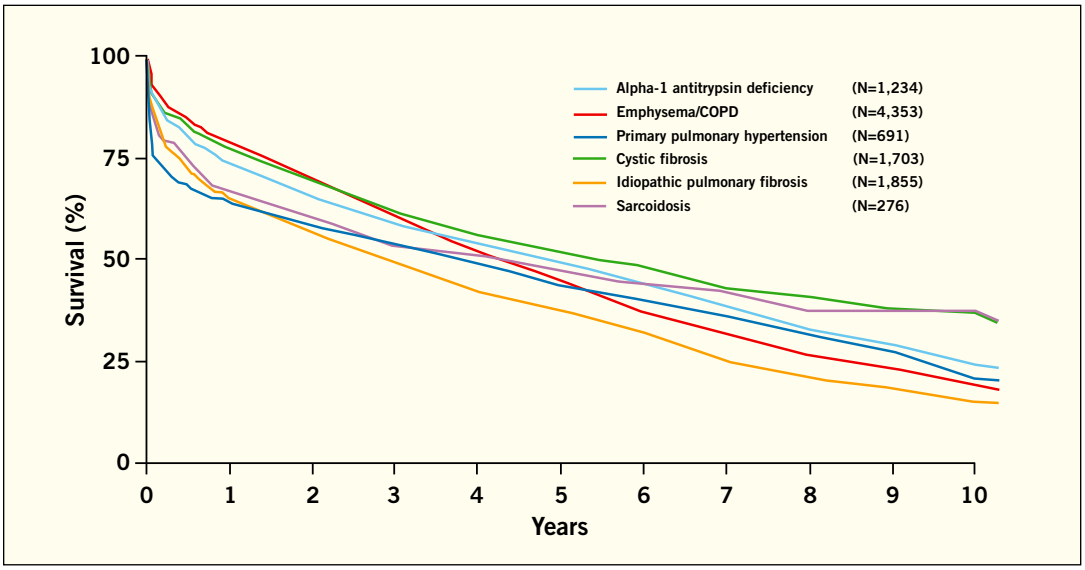

Figure 1. UNOS/ISHLT registry data showing actuarial survival for all lung transplant patients by diagnosis (January 1990 to June 2001). Note higher early mortality for recipients with primary pulmonary hypertension compared with other diagnoses. From www.ishlt.org.

data from the National Institutes of Health primary pulmonary hypertension registry.[25] At this point, however, it makes little sense to compare the outcome of lung transplantation with that of medical therapy. Lung transplantation should be utilized only for patients in whom medical therapy fails.

Functional Outcomes of Transplantation

Functional outcomes have been analyzed by the International Society for Heart and Lung Transplantation registry report.[35] At 3 years post transplant, 89.6% of recipients reported no activity limitations, 9.3% were able to perform activity with some assistance, and 1% required total assistance. Despite the functional improvements achieved with transplantation, only a minority of patients (29.1%) were working full time by 3 years post transplant. A majority of patients (54.8%) required repeat hospitalization in the first year of follow-up, although in the third postoperative year this fell to 38.2%. The most common reason for repeat hospitalization was allograft rejection and infection.

Quality of Life Following Transplantation

Despite widespread use of lung transplantation as a therapeutic modality, few published studies assess quality of life in recipients of this procedure. Gross and colleagues[36] documented overall improvement in quality of life following lung transplantation assessed by the Medical Outcomes Health Survey (MOS)-20 health profile. Over the long term, the benefit persists except in those patients who develop chronic rejection. Although significant benefits in exercise tolerance, pulmonary function, and quality of life exist following lung transplantation, only a minority of patients return to work on a full-time basis. The reasons why so few recipients return to work are not well known. Following transplantation the majority of patients reach functional levels that should not limit their physical ability to work in a variety of occupations. It is true, however, that many transplant recipients are unable to work because of financial constraints. For some the choice of returning to work means giving up disability insurance benefits that cover their long-term medications and post-transplant medical care.

Cost of Lung Transplantation

The financial cost of lung transplantation is not trivial. In fact, the high cost has been a motivating factor for Medicare and other third party payers to offer reimbursement for this procedure only to approved centers of excellence. Ramsey et al[37] outlined the overall costs of lung transplantation for the University of Washington Medical Center. The average charges for the procedure and immediate postoperative care were $164,989 (median $152,071). The post-transplant average monthly charges during the first 6 months were $16,628; in the second 6 months they were $5,440, but fell to $4,525 thereafter. This compared to the average monthly charges for patients on the waiting list of $3,395. Although these figures come from a single center, they do not differ substantially from reports of other centers.[38,39]

Summary

All potential lung transplantation candidates with PAH should be considered for treatment with epoprostenol where available. In the United States, patients should be listed for transplantation at initiation of therapy; the response to epoprostenol should be reviewed at regular intervals and dosage increased as tolerated. Patients who respond well should be removed from the transplant list and monitored for continued responsiveness. For those in whom medical therapy fails, lung transplantation remains a viable option. Despite the potential for improved survival and function, this procedure is associated with several limitations. These include the lack of available donor lungs, the morbidity and mortality associated with the surgery, high financial cost, lifelong need for immunosuppression, and the risk of infection and rejection. Research is under way to develop better methods for organ tolerance without the need for potent, nonspecific immunosuppression. Potential candidates for lung transplantation should be referred to transplant centers early to maximize their chance for survival.

References

1. Hosenpud JD, Bennett LE, Keck BM, Fiol B, Novick RJ. The registry of the International Society for Heart and Lung Transplantation: fourteenth official report-1997. *J Heart Lung Transplant.* 1997;16:691-694.
2. Reitz BA, Wallwork JL, Hunt SA, Pennock JL, Billingham ME, Oyer PE, et al. Heart-lung transplantation: successful therapy for patients with pulmonary vascular disease. *N Engl J Med.* 1982;306(10):557-564.

3. Low DE, Trulock EP, Kaiser LE. Morbidity, mortality, and early results of single versus bilateral lung transplantation for emphysema. *J Thorac Cardiovasc Surg.* 1992;103:1119-1126.
4. Mal H, Sleiman C, Jebrak G, Messian O, Dubois F, Darne C, et al. Functional results of single-lung tranplantation for chronic obstructive lung disease. *Am J Respir Crit Care Med.* 1994;149(6):1476-1481.
5. Trulock EP. Lung transplantation for COPD. *Chest.* 1998;113(suppl 4):269s-276s.
6. Rubin LJ, Nicod P, Hillis LD, Firth BG. Treatment of primary pulmonary hypertension with nifedipine. A hemodynamic and scintigraphic evaluation. *Ann Intern Med.* 1983;99(4):433-438.
7. Rich S, Brundage BH. High-dose calcium channel-blocking therapy for primary pulmonary hypertension: evidence for long-term reduction in pulmonary arterial pressure and regression of right ventricular hypertrophy. *Circulation.* 1987;76(1):135-141.
8. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. *N Engl J Med.* 1992;327(2):76-81.
9. Rubin LJ, Mendoza J, Hood M, McGoon M, Barst R, Williams WB, et al. Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomized trial. *Ann Intern Med.* 1990;112(7):485-491.
10. Conte JV, Gaine SP, Orens JB, Harris T, Rubin LJ. The influence of continuous intravenous prostacyclin therapy for primary pulmonary hypertension on the timing and outcome of transplantation. *J Heart Lung Transplant.* 1998;17(7):679-685.
11. Rich S. Medical treatment of primary pulmonary hypertension: a bridge to transplantation? *Am J Cardiol.* 1995;75(3):63A-66A.
12. Gaine SP, Rubin LJ. Medical and surgical treatment options for pulmonary hypertension. *Am J Med Sci.* 1998;315(3):179-184.
13. American Thoracic Society: Medical Section of the American Lung Association. International guidelines for the selection of lung transplant candidates. *Am J Respir Crit Care Med.* 1998;158:335-339.
14. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med.* 1991;115(5):343-349.
15. Rich S, Levy PS. Characteristics of surviving and nonsurviving patients with primary pulmonary hypertension. *Am J Med.* 1984;76(4):573-578.
16. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Primary pulmonary hypertension. A national prospective study. *Ann Intern Med.* 1987;107(2):216-223.
17. Kadikar A, Maurer J, Kesten S. The six-minute walk test: a guide to assessment for lung transplantation. *J Heart Lung Transplant.* 1997;16(3):313-319.
18. Fuster V, Steele PM, Edwards WD, Gersh BJ, McGoon MD, Frye RL. Primary pulmonary hypertension: natural history and the importance of thrombosis. *Circulation.* 1984;70(4):580-587.
19. Barst RJ, Rubin LJ, McGoon MD, Caldwell EJ, Long WA, Levy PS. Survival in primary pulmonary hypertension with long-term continuous intravenous prostacyclin. *Ann Intern Med.* 1994;121(6):409-415.
20. Shapiro SM, Oudiz RJ, Cao T, Romano MA, Beckmann XJ, Georgiou D, et al. Primary pulmonary hypertension: improved long-term effects and survival with continuous intravenous epoprostenol infusion. *J Am Coll Cardiol.* 1997;30(2):343-349.
21. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med.* 1996;334(5):296-302.
22. Whyte RI, Robbins RC, Altinger J, Barlow CW, Doyle R, Theodore J, et al. Heart-lung transplantation for primary pulmonary hypertension. *Ann Thorac Surg.* 1999;67(4):937-941.
23. Bando K, Armitage JM, Paradis IL, Keenan RJ, Hardesty RL, Konishi H, et al. Indications for and results of single, bilateral, and heart-lung transplantation for pulmonary hypertension. *J Thorac Cardiovasc Surg.* 1994;108(6):1056-1065.
24. Bando K, Keenan RJ, Paradis IL, Konishi H, Komatsu K, Hardesty RL, et al. Impact of pulmonary hypertension on outcome after single-lung transplantation. *Ann Thorac Surg.* 1994;58(5):1336-1342.
25. Pasque MK, Trulock EP, Cooper JD, Triantafillou AN, Huddleston CB, Rosenbloom M, et al. Single lung transplantation for pulmonary hypertension. Single institution experience in 34 patients. *Circulation.* 1995;92(8):2252-2258.
26. Hosenpud JD, Bennett LE, Keck BM, Boucek MM, Novick RJ. The Registry of the International Society for Heart and Lung Transplantation: seventeenth official report-2000. *J Heart Lung Transplant.* 2000; 19(10):909-931.
27. Levine SM, Jenkinson SG, Bryan CL, Anzueto A, Zamora CA, Gibbons WJ, et al. Ventilation-perfusion inequalities during graft rejection in patients undergoing single lung transplantation for primary pulmonary hypertension. *Chest.* 1992;101(2):401-405.
28. Chaparro C, Kesten S. Infections in lung transplant recipients. *Clin Chest Med.* 1997;18(2):339-351.
29. Maurer JR, Tullis DE, Grossman RF, et al. Infectious complications following isolated lung transplantation. *Chest.* 1992;101:1056-1059.
30. Dolonish M, Rossm C, Chambers C, et al. Mucociliary function in patients following single or lung-heart transplantation. *Am Rev Respir Dis.* 1987;135:A363.
31. Armitage J, Kormos R, Stuart R, Fricker F, Griffith BP, Nalesnik M, et al. Posttransplant lymphoproliferative disease in thoracic organ transplant patients: ten years of cyclosporine-based immunosuppression. *J Heart Lung Transplant.* 1991;10:877-887.
32. US Department of Health and Human Services H. 2003 Annual report of the US Scientific Registry for Transplant Recipients and the Organ Procurement and Transplantation Network: Transplant data 1989-2001. 2003. Rockville, MD, UNOS, Richmond, VA.
33. Trulock EP, Edwards LB, Taylor DO, Boucek MM, Mohacsi PJ, Keck BM, et al. The Registry of the International Society for Heart and Lung Transplantation: twentieth Official adult lung and heart-lung transplant report-2003. *J Heart Lung Transplant.* 2003;22(6):625-635.
34. Yagi K, Liu C, Bando T, et al. Inhibition of reperfusion injury by human thioredoxin (adult T-cell leukemia derived factor) in canine lung rransplantation. *J Thorac Cardiovasc Surg.* 1994;108:913.
35. Hosenpud JD, Bennett LE, Keck BM, Fiol B, Boucek MM, Novick RJ. The Registry of the International Society for Heart and Lung Transplantation: fifteenth official report-1998. *J Heart Lung Transplant.* 1998;17(7):656-668.
36. Gross C, Savik K, Bolman M, Hertz MI. Long-term health status and quality-of-life outcomes of lung transplant recipients. *Chest.* 1995;108:1587-1593.
37. Ramsey S, Patrick D, Albert R, Larson E, Wood D, Raghu G. The cost effectiveness of lung transplantation. *Chest.* 1995;108(6):1594-1601.
38. Reemtsma K, Gelijns A, Sisk J, et al. Supporting future surgical innovation lung transplantation as a case study. *Ann Surg.* 1993;218:465.
39. Maurer JR. Costs of lung transplant in Canada. *J Heart Lung Transplant.* 1996;13:S70.