Bronchiolitis following transplantation is bronchiolitis obliterans, with an incidence of 30 to 50%. Bronchiolitis obliterans presents clinically with an obstructive deterioration in pulmonary function and little change in chest radiograph appearance, and it develops > 3 to 6 months following transplantation, usually at a mean of 16 to 20 months. Pathologically, there is obliteration of the terminal bronchioles (ie, constrictive bronchiolitis). Because it is difficult to make a reliable histologic diagnosis of bronchiolitis, the ISHLT has defined a bronchiolitis obliterans syndrome (BOS) staging system based on a deterioration of pulmonary function (FEV₁ reported as a percentage of pretransplant baseline values) with the performance of bronchoscopy to exclude alternate diagnoses such as acute rejection, infection, or anastomotic complications. The staging system is further subdivided by the presence or absence of the histologic confirmation of bronchiolitis. Since the sensitivity of transbronchial biopsy for the pathologic diagnosis of BOS can be as low as 15%, in the majority of cases the diagnosis of BOS is made based on pulmonary function changes alone.

The etiology of BOS remains unknown, although numerous risk factors have been postulated. Probable risk factors for BOS include acute rejection, lymphocytic bronchitis, and cytomegalovirus (CMV) pneumonitis. Other potential or hypothetical risk factors include CMV infection, organizing pneumonia, non-CMV infection, older donor age, prolonged ischemic time, human leukocyte antigen mismatching, and donor antigen-specific reactivity.

As illustrated earlier in the ISHLT survival data, there is increased survival in all patients undergoing BLT vs those undergoing SLT procedures by 3 years following transplantation. The reasons for this are unclear but have been speculated to be due to greater pulmonary function reserve in BLT recipients. The article in this issue of CHEST by Hadjiliadis et al (see page 1168) proposes a hereto unreported risk factor for BOS and postulates a hypothesis to explain the survival differences noted.

This is a retrospective study from a single large lung transplant center comparing a group of patients undergoing BLT to those undergoing SLT with respect to the development of BOS. When numerous risk factors were subjected to several types of multivariate analyses, the authors found the following risk factors to correlate with the development of BOS: acute rejection scores; the number of human leukocyte antigen mismatches; CMV mismatch; and, the focus of the article, the type of lung transplant procedure performed. In fact, procedure type was found to be an independent risk factor for BOS in all of the analyses conducted. The authors found that, at least in a relatively short follow-up period (median follow-up, 2.4 years; range, 1.5 to 4 years), the BLT group had a significantly lower incidence of developing BOS (31.7%) than did the SLT group (49.3%).

The other BOS risk factors identified in this analysis have been reported previously in multiple studies. This is the first report of a difference in the incidence of BOS between patients who have undergone SLT procedures and those who have undergone BLT procedures. Since the cellular and immu-

**Lung Transplantation and Bronchiolitis Obliterans Syndrome**

**Are Two Lungs Better Than One?**

The current survival rates for lung transplant recipients are 72%, 56%, and 43%, respectively, at 1, 3, and 5 years, as reported by the registry of the International Society of Heart and Lung Transplantation (ISHLT). These data can be further subanalyzed based on single-lung transplant (SLT) vs bilateral lung transplant (BLT) procedures. SLT survival rates were 71%, 54%, and 40% at 1, 3, and 5 years, respectively. BLT survival rates were 72%, 58%, and 48% at 1, 3, and 5 years, respectively.

The leading cause of mortality after the first year following transplantation is bronchiolitis obliterans, with an incidence of 30 to 50%. Bronchiolitis obliterans has become the *sine qua non* for chronic lung rejection in the lung transplant population. Bronchiolitis obliterans presents clinically with an obstructive deterioration in pulmonary function and little change in chest radiograph appearance, and it develops > 3 to 6 months following transplantation, usually at a mean of 16 to 20 months. Pathologically, there is obliteration of the terminal bronchioles (ie, constrictive bronchiolitis). Because it is difficult to
nologic mechanisms for these findings are difficult to postulate, what are the possible clinical explanations for these findings? One of the most important may hinge on the diagnosis of BOS itself. Only a small minority of patients in the total study group had a histologic diagnosis of bronchiolitis (13.9%) with changes in pulmonary function serving as the “gold standard” for the diagnosis of BOS in the majority of the patients, as in other BOS risk factor studies. Are there other factors that could account for a deterioration in pulmonary function that would not be diagnosed by endobronchial inspection (eg, anastomotic narrowing), BAL (eg, infection), or transbronchial biopsy (eg, acute rejection or infection)? In this study, there was a significant difference in the predominant transplant diagnosis in patients in the SLT and BLT groups. The majority of SLT procedures were performed in patients with COPD (72.7%), and the majority of BLT procedures were performed in patients with cystic fibrosis (45.2%). However, even when underlying lung disease was controlled for in the statistical analysis, procedure type remained a significant risk factor for BOS.

In SLT procedures performed for COPD, hyperinflation of the native lung resulting in extrinsic compression of the lung graft, dyspnea, and deterioration in pulmonary function, as can be seen with the development of BOS, has been well-documented in several studies to occur over time. Therefore, since the majority of the SLT group in this study underwent transplantation for COPD, perhaps native lung hyperexpansion and not BOS was accounting for the changes in pulmonary function in some of these patients. In several studies, lung volume reduction surgery of the hyperinflated native lung has corrected this problem. At least one study has attempted to distinguish between these two etiologies of worsening pulmonary function in SLT recipients who have COPD by performing measurements of lung resistance during inspiration. The authors found that patients with elevated lung resistance during inspiration had airway obstruction due to intrinsic airway disease such as BOS rather than to intrinsic restriction by a hyperinflated native lung.

To address this question, the logical study design would be to compare patients with a single diagnosis who were undergoing SLT to those patients undergoing BLT. Because many centers prefer to perform BLT procedures in their younger COPD patients and SLT in their older COPD patients due to increased pulmonary reserve in the BLT group, several studies have made this comparison. The majority of these studies found that younger COPD patients (ie, those < 45 to 60 years of age) undergoing BLT have improved survival rates in comparison to COPD patients undergoing SLT, which likely is due to increased pulmonary reserve, with no difference in the incidence of BOS between the two procedure groups. A small subanalysis performed by the authors of the current study examining only those patients who had received transplants for treatment of emphysema found differences in the incidence of BOS in the SLT and BLT patient groups in contrast to the results of the studies mentioned previously.

Another explanation for the differences in the incidence of BOS between these two groups, as pointed out by the authors, is that the BLT recipients have more pulmonary reserve than the SLT group and, therefore, present with clinical deterioration later than do the SLT recipients. In other words, if the BOS diagnosis in the majority of these patients is based largely on a deterioration in FEV₁, then the SLT recipients will reflect this change earlier in the posttransplant course, since the presence of bronchiolitis obliterans in the transplanted lung would lead to a larger decrease in the overall FEV₁.

Other differences between the SLT and BLT groups found by the authors included difference in mean ages (the BLT group was significantly younger than the SLT group). In the current study, procedure type remained a significant risk factor even after controlling for recipient age. Furthermore, the two comparison groups underwent transplantation in different transplant eras with some changes in the immunosuppressive protocol, including the introduction of induction immunosuppression and the routine use of mycophenolate mofetil as part of the maintenance immunosuppressive protocol. These factors also could contribute to the differences found in this study.

Some of the problems with the diagnosis of BOS have been highlighted by the ISHLT in a recently published proposed revision of the BOS staging system. This new staging system proposes an earlier category of BOS called BOS0-potential, which is based on a decrease in mid-flows of forced expiratory flow to ≤ 75% of baseline values and/or an FEV₁ of 81 to 90% of baseline values. This may aid in identifying those patients who are potentially at risk for BOS and may allow for an earlier diagnosis of BOS, particularly in the BLT population. But, it also may lead to a more confounding situation, with minor changes in the native lung in SLT patients with COPD presenting with alterations in small airway function earlier than in BLT recipients. Should all SLT recipients with COPD be subjected to detailed and complex physiologic testing in order to isolate physiologic changes in airway resistance to the transplanted lung? Clearly, a reliable test to definitively diagnose BOS, be it in SLT or BLT recipients, continues to elude discovery.

www.chestjournal.org

CHEST / 122 / 4 / OCTOBER, 2002

1113
Traditional indications for SLT procedures include the following: COPD due to tobacco use or alpha1-antitrypsin deficiency, interstitial lung disease due to pulmonary fibrosis, and sarcoidosis among others and, at a few centers, pulmonary hypertension. Indications for BLT include septic or suppurative lung diseases such as cystic fibrosis or bronchiectasis, and at some centers, pulmonary hypertension and younger patients with COPD.

If the findings of the study in this issue of CHEST are confirmed, then the ethical and moral implications are significant. SLT has several advantages over BLT. It is thought by some surgeons to be technically easier than BLT, the procedure time is shorter, there is less frequent need for cardiopulmonary bypass, and, most importantly, one donor can provide single lungs to two recipients, alleviating the serious shortage of donor organs, which remains the rate-limiting step to the number of transplant procedures performed annually. This has to be weighed against BLT characteristics such as improved pulmonary function, better survival, the ability to use marginal lung donors, and as raised in the current article, the decreased risk of BOS in BLT recipients, which are raised in the current article. Until the current shortages of donor lungs abate (a national problem) or until these questions are clearly answered in future studies, I would recommend continuing the performance of BLT procedures in those groups of patients with septic lung disease that require a BLT procedure and continuing to perform SLT procedures in those groups traditionally treated with SLTs.

Stephanie M. Levine, MD, FCCP
San Antonio, TX

Dr. Levine is Professor of Medicine at The University of Texas Health Science Center at San Antonio, and is affiliated with the South Texas Veterans Health Care System.

Correspondence to: Stephanie M. Levine, MD, FCCP, Associate Professor of Medicine, Division of Pulmonary Diseases/Critical Care Medicine, Department of Medicine, The University of Texas Health Science Center, 7703 Floyd Curl Dr, San Antonio, TX 78229; e-mail: levines@uthscsa.edu

REFERENCES
2 Trulock EP. Lung transplantation. Am J Respir Crit Care Med 1997; 156:789–818

Telesupport
Just Reach Out and Touch Someone

Lung transplantation is an accepted therapeutic option for patients who have a number of end-stage pulmonary diseases. In calendar year 1999, the United Network for Organ Sharing reported1 that 877 lung transplants and 49 heart-lung transplants had been performed in the United States alone, with a waiting list of 3,491 persons. During the same time period, > 2,000 transplants were performed worldwide.2 About 76% of lung transplant recipients will survive through the first year, and 56% make it to 3 years.1 When assessing the efficacy of a given intervention on outcomes for any end-stage organ disease, there is a growing emphasis not only on improvements in survival, but also on the associated health-related quality of life (HRQOL). Incorporat-