Respiratory Failure Early After Lung Transplantation

Now That We Know the Extent of the Problem, What Are the Solutions?

Over the last 20 years, lung transplantation has emerged as a valid treatment option for a wide range of advanced lung diseases. Surgical advances combined with newer immunosuppressant medications have improved outcomes; however, both the short-term and long-term survival after lung transplant continues to lag behind other solid-organ transplants. Survival for lung transplant recipients at 1 year, 3 years, and 5 years is approximately 76%, 58%, and 47%, respectively. Early respiratory failure and death after lung transplant can result from airway complications, hyperacute rejection, acute rejection, infection, or ischemia/reperfusion lung injury (IRLI). Graft failure secondary to bronchial dehiscence is now rare with improved surgical techniques. Hyperacute rejection, infrequently described in lung transplantation, results from preformed antibodies that target antigens in the allograft vascular endothelium and cause extensive thrombosis and complement activation. Acute rejection occurs in > 60% of lung recipients despite current immunosuppressive protocols, but usually responds to augmented immunosuppression and rarely leads to early graft loss. Infectious complications, such as bacterial pneumonia or cytomegalovirus, have been described as a common etiology of respiratory failure and mortality in the early posttransplant period. IRLI or reimplantation response is characterized by the development of bilateral pulmonary infiltrates, declining lung compliance, and worsening of gas exchange in the immediate posttransplant period after exclusion of rejection, infection, and heart failure. Severe IRLI has been reported to occur in 15 to 30% of patients. Despite the increasing experience with lung transplantation, all of these problems contribute to the development of early respiratory failure and a 1-year mortality of approximately 25%.

In this issue of CHEST (see page 165), Chatila et al have attempted to determine the incidence and attributable mortality of acute respiratory failure from any cause after lung transplantation. They studied 80 consecutive patients who underwent single or bilateral lung transplantation between 1994 and 1999 at a single center. Postoperative respiratory failure was defined as the need for mechanical ventilation for > 48 h after transplant or the need for reintubation prior to hospital discharge. They found that 44 of 80 lung transplant recipients (55%) acquired acute respiratory failure. In-hospital mortality was significantly higher among patients who acquired acute respiratory failure compared to those who did not, 45% vs 3%. More than 50% of the episodes of acute respiratory failure were attributable to IRLI, and < 10% were attributed to infectious etiologies. Allograft rejection and airway complications contributed to 5% and 11% of the episodes of respiratory failure, respectively. Similar to prior studies, they found that the development of IRLI was associated with an increased incidence of acute respiratory failure and in-hospital mortality.

Based on the results of Chatila et al, it appears the main cause of early morbidity and mortality after lung transplant has shifted away from infections to...
IRLI. Improved antimicrobial prophylactic regimens and diagnostic testing are likely to have contributed to a decrease in the incidence of infections in the early posttransplant period. In contrast, the incidence of IRLI after lung transplant may be increasing. The exact pathophysiology of IRLI is unknown. Up-regulation of inflammatory cytokines such as interleukin-83 or matrix metalloproteinase 94 may occur as a result of donor lung injury or surgical trauma. Nuclear factor-κB regulates many genes that are responsible for the development of acute inflammation in this setting, and represents a promising target for intervention. In a porcine model of lung transplantation IRLI, an inhibitor of nuclear factor-κB significantly improved lung function at 4 h compared to control subjects.5 Preformed antibodies directed against endothelial cell human leukocyte antigens (HLAs) may also contribute to acute lung injury. An elevated level of panel reactive antibodies against HLA has been shown to increase the incidence of early graft dysfunction in lung and other solid-organ recipients.6 The improved sensitivity of flow cytometry has resulted in an increasing number of lung transplant recipients who are recognized to have antibodies against donor HLAs.6 Early identification of sensitized recipients may provide an opportunity for intervention. Inflammatory cytokines produced from leukocytes and the presence of preformed antibodies against HLAs represent two potential mechanisms of pathophysiologic injury that warrant further study in the prevention of IRLI.

Prior studies have found a greater incidence of IRLI associated with pulmonary hypertension,7 cardiopulmonary bypass (CPB),8 donor characteristics,9 and ischemia time,10 but the results have been inconsistent. This study by Chatilla et al identified right ventricular (RV) dysfunction as a preoperative variable that is independently associated with both the development of acute respiratory failure and increased in-hospital mortality. The finding that RV dysfunction was associated with a greater incidence of acute respiratory failure in this study is not surprising. Prior studies have shown that there is a higher early mortality associated with lung transplantation for pulmonary hypertension as compared to other native diseases; however, the long-term outcomes are comparable to those of other patients.7 It is unclear from the data presented how many patients with primary or secondary pulmonary hypertension underwent single vs bilateral transplantation. Furthermore, the use of a subjective grading for RV dysfunction may have limited the ability to determine if there is a critical level of reduced RV function from which recovery is not possible.

Chatilla et al also found that the need for CPB as well as bilateral lung transplantation were associated with the greatest risks of respiratory failure in univariate analysis. The “postperfusion lung syndrome” associated with CPB has been noted in a wide range of patient populations including lung transplant recipients.8 It is believed that CPB can lead to complement activation and increased levels of inflammatory cytokines that produce capillary leak and noncardiogenic pulmonary edema. Both IRLI and postperfusion lung syndrome have similar clinical and pathologic manifestations. Although bilateral lung transplantation was also associated with an increased risk of acute respiratory failure in univariate analysis, neither CPB nor bilateral transplant was significant in the multivariate model. A recent review of the United Network of Organ Sharing lung transplant database of 2,260 lung transplant recipients for emphysema between 1991 and 1997 compared the mortality between single lung and double lung transplants. They found no difference in the 30-day mortality between the two groups, and the long-term survival data favored bilateral lung transplants for individuals < 60 years of age.11 Thus, the finding of increased short-term morbidity and mortality associated with bilateral lung transplant at this single center needs to be interpreted with caution. It may be a marker of other high-risk characteristics that influence the type of operation performed at the center or simply a result of random statistical chance, given the rather large number of analyses performed in the relatively small patient population.

Chatilla et al have shown that short-term mortality after lung transplantation continues to be high and that the main cause of early allograft dysfunction has shifted from infections to IRLI. While this study does a good job at identifying and describing the problems of the early posttransplant time period, several limitations make it unable to identify important risk factors for the different types of complications. This study included a diverse patient population with many different underlying lung diseases, which suffered a wide range of complications that are all grouped together as acute respiratory failure. The role of RV dysfunction, pulmonary hypertension, or CPB in contributing to IRLI remains intriguing. Future multicenter or registry studies that look at more focused populations based on underlying disease and specific complications will be better suited to define the important and potentially modifiable risk factors for IRLI. Additional translational research is also needed to better define the basic mechanisms that determine why some patients acquire fatal IRLI immediately after transplant and others are exubated within 48 h. These studies will need to accurately identify both clinical and biological risk factors and also better define the different pathologic processes that cause early allograft dys-
function and are currently grouped together as IRLI. Relative to other solid-organ transplants, lung transplantation continues to be in its infancy. The short-term and long-term mortality rates are higher than kidney, liver, or heart transplants. This important study by Chatilla et al points out some of the persistent problems facing the field of lung transplantation. It raises many questions that need to be answered in order to improve on the high morbidity and mortality that we encounter today.

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End-of-Life Care and Eudaemonia

How do we die? Where do we die? Who decides the answers to these questions? These questions and a few others come to mind when reviewing the article in this month’s CHEST (see page 266), “Impact of a Proactive Approach To Improve End-Of-Life Care in a Medical ICU,” by Guzman and Campbell. Why are studies like this done at medical centers and not at community hospitals? What do patients expect from us at the end of life? Where has the joy in medicine gone?

In their article, Guzman and Campbell looked at end-of-life care for critically ill patients with global cerebral ischemia post-cardiopulmonary resuscitation and multiple organ system failure. In a comparative study at a university hospital medical ICU, they looked at issues related to end-of-life care in critically ill patients with very poor prognoses. They found that by utilizing a prospective, proactive approach to these patients with a palliative care team there was a decreased hospital length of stay with a potential for cost savings. Another major point involved the decreased time between the identification of the poor prognosis and the establishment of comfort care-only measures.

While one may be able to quibble with their overall methods and statistics, my primary goal will be to further the cause for more studies dealing with end-of-life care. As the authors mentioned, the small numbers in their study make extrapolation of these data somewhat tenuous. However, while it is not a definable problem with this specific article, I believe that we need a major shift of emphasis in articles such as this. This study was conducted at a university hospital that had attending physicians, fellows, other house staff, medical students, and an established palliative care team. Since most patients in this country who are critically ill are actually cared for in a different environment, that is, in the ICU of a community hospital, there should be a means of pairing studies such as this with a community hospital. This would have a tremendous potential benefit. It could serve to break down the town-and-gown mentality, it could raise the level of care and interest in community hospitals, and any meaningful data or conclusions from such studies would be more generalizable to the medical community and therefore to more patients. In this way, we would be able to more immediately and effectively use these data rather than waiting for the study that applies to one’s particular environment. Combining academic resources with an increasing number of excellent, resourceful, and progressive community hospitals could be a practical approach. It has been thought that a

References