Acute Pulmonary Edema After Lung Transplantation*

The Pulmonary Reimplantation Response

Saeed U. Khan, MD; Joseph Salloum, MD; Peter B. O’Donovan, MB BCh; Edward J. Mascha, MS; Atul C. Mehta, MD, FCCP; Michael A. Matthay, MD, FCCP; and Alejandro C. Arroliga, MD, FCCP

Background: Although the development of noncardiogenic pulmonary edema or pulmonary reimplantation response (PRR) after lung transplantation has been well described, the incidence has not been established and the relationship of PRR to clinical risk factors has not been analyzed.

Study objectives: (1) To describe the incidence of PRR in lung transplant recipients, (2) to identify the predictors of PRR, (3) to examine the correlation of suspected predictors with the severity of PRR, and (4) to evaluate the impact of PRR on morbidity and mortality of lung transplant recipients.

Design: Retrospective review of clinical records and radiographic studies.

Setting: Tertiary care referral center.


Methods: Review of clinical records and postoperative chest radiographs of all lung transplant recipients to identify patients who experienced PRR. Chest radiographs of patients with PRR were graded for severity on a scale of 0 (none) to 5 (very severe). Demographic, pre- and perioperative factors were also evaluated along with short- and long-term survival of patients with PRR.

Results: Fifty-six of 99 lung transplant recipients (57%) experienced PRR. The median ischemia time of patients with and without PRR was 168 and 180 min, respectively (p = 0.62). The incidence of PRR was 51% in patients without preoperative pulmonary hypertension, 78% in mild to moderate pulmonary hypertension, and 58% in patients with severe pulmonary hypertension (p = 0.10). Incidence and severity of PRR was similar in patients receiving right, left, or double-lung transplantation. Similarly, age and sex of the recipients and underlying lung disease did not affect the incidence or severity of PRR. The incidence and severity of PRR was higher in patients undergoing cardiopulmonary bypass during lung transplantation. Patients with PRR had prolonged duration of mechanical ventilation and ICU stay. Overall, PRR did not affect the survival of the patients. However, survival of female lung transplant recipients was significantly better than male recipients (median survival, 60 vs 21 months; p = 0.02).

Conclusions: Acute pulmonary edema or PRR occurs frequently (57%) after lung transplantation. In this series, PRR was not associated with a prolonged ischemia time, preoperative pulmonary hypertension, the type of lung transplant, underlying lung disease, or age or sex of recipients. However, use of cardiopulmonary bypass during surgery was associated with increased incidence and severity of PRR. Also, the development of PRR resulted in prolonged mechanical ventilation and a longer ICU stay, but did not affect survival. Female lung transplant recipients survived significantly longer than male recipients. The reason for this difference in survival is unclear.

CHEST 1999; 116:187–194

Key words: acute pulmonary edema; lung transplantation; pulmonary reimplantation response

Abbreviations: CF = cystic fibrosis; CI = confidence interval; FIO₂ = fraction of inspired oxygen; IL = interleukin; IPF = idiopathic pulmonary fibrosis; PAP = pulmonary artery pressure; PPH = primary pulmonary hypertension; PRR = pulmonary reimplantation response
Lung transplantation has become an established therapeutic option for end-stage lung disorders refractory to medical management. Despite advances in understanding and treatment of patients after lung transplantation, the clinical course can still be complicated by ischemic injury to the allograft, resulting in noncardiogenic pulmonary edema, infections, acute and chronic rejection, and drug toxicity.

The occurrence of noncardiogenic pulmonary edema in the immediate postoperative period after lung transplantation is termed pulmonary reimplantation response (PRR). It is thought to be an ischemic vascular injury of the allograft that results in increased protein permeability of the lung microcirculation after reperfusion, which can result in interstitial and alveolar edema.1

Although PRR has been studied extensively in animals,2–6 limited information is available after lung transplantation in humans. For example, the incidence of PRR has not been established. Similarly, potential clinical predictors such as duration of ischemia time, preoperative pulmonary hypertension, underlying lung disease, and single-lung vs double-lung transplantation have not been well evaluated.

Therefore, there were four objectives of this study: to determine the incidence of PRR in a large number of consecutive lung transplant recipients, to determine whether any clinical factors predict the development of PRR, to examine the correlation of potential clinical predictors with the severity of PRR, and to evaluate the impact of PRR on morbidity and mortality of lung transplant recipients.

**Materials and Methods**

The clinical records of all lung transplant recipients at The Cleveland Clinic Foundation were reviewed between February 1990 and October 1995. Standard criteria were used in recipient selection.7,8 All recipients were ≤ 65 years old with chronic progressive end-stage pulmonary disease with projected life expectancy of <12 to 18 months. Preoperative right heart catheterization was performed in all candidates age ≥ 50 years old and in those with suspected pulmonary hypertension on echocardiogram. Bilateral lung transplantation was used in patients with cystic fibrosis (CF), bilateral bronchiectasis, and in some patients with primary pulmonary hypertension (PPH). In case of single-lung transplantation, the side to be transplanted was determined primarily by quantitative ventilation-perfusion scintigraphy: the lung with a poorer ventilation-perfusion ratio was usually transplanted. The decision to use cardiopulmonary bypass during surgery was based on the presence of preoperative pulmonary hypertension and the response of arterial oxygen tension, arterial carbon dioxide tension, elevation of pulmonary artery pressure (PAP), and reduction in cardiac index during one-lung ventilation.

**Donor Selection and Lung Preservation**

Standard donor selection criteria were applied.9 Organ harvesting was started with infusion of prostaglandin E1 via a central vein beginning 15 min before aortic cross-clamping, using 10 ng/kg/min prostaglandin E1 and gradually increasing the rate of infusion according to BP tolerance to a maximum of 80 ng/kg/min. Lung perfusion cooling was performed using modified Euro-Collins solution at 4°C into the main pulmonary artery. At least 4 L Euro-Collins solution was used for the flush. Ventilation of the donor was continued with room air during lung perfusion. The trachea was stapled with the lungs two-thirds inflated. The lung was removed and placed in a sterile plastic bag filled with Euro-Collins solution at 4°C.

Transplantation of the lung in the recipient was performed using the standard technique for single and bilateral sequential lung transplant.10,11 Systolic arterial and venous pressures, cardiac output, PAP, and arterial blood gases were closely monitored during the surgical procedure. In single-lung transplantation, allograft ischemia time was measured from aortic cross-clamping at organ procurement to the time of reperfusion after completion of the lung transplant. In bilateral sequential transplantation, ischemia time of the second lung was used.

**Immunosuppression**

Intravenous methylprednisolone (500 mg) was given perioperatively immediately before graft perfusion. Standard induction triple-drug immunosuppression consisting of cyclosporin (3 to 6 mg/kg), azathioprine (2.5 mg/kg), and methylprednisolone (125 mg every 8 h for 48 h followed by 20 mg bid until resumption of oral medication) was initiated. The dose of azathioprine was adjusted to maintain the WBC count > 4,000/μL.

**Postoperative Management**

Routine postoperative intensive care management was performed.12 All patients had pulmonary artery catheters for measuring central venous pressure, PAP, mean pulmonary artery occlusion pressure, and cardiac output. Careful attention was given to fluid balance to avoid fluid overload. Prophylactic antibiotics were started perioperatively and ganciclovir was used in recipients with cytomegalovirus mismatch (donor positive/recipient negative and donor negative/recipient positive). Weaning from the ventilator was initiated as early as possible after the surgery. Chest radiographs were obtained on the day of surgery and at least once daily thereafter during the ICU stay. All patients had bronchoscopy at least on alternate days to remove secretions and to examine the bronchial anastomotic site. Tracheal aspirate was obtained daily and examined for infection. Bronchoscopy was also performed to do a BAL and to obtain protected brush specimen for the diagnosis of infection whenever a new lung infiltrate was identified on chest radiographs. Blood cultures were also done daily during the ICU stay. Infection was suspected clinically when lung infiltrates were associated with fever and hypoxemia. Transbronchial biopsies of the allograft, in the first postoperative week to diagnose rejection, were done at the time.
discretion of the lung transplant physician taking care of the patient. Patients with an acute rejection diagnosis were treated with bolus methylprednisolone of 15 mg/kg (maximum, 1.0 g) IV once daily for 3 days after excluding infection.

Identification of PRR

All chest radiographs in the first 5 postoperative days were reviewed by a chest radiologist (P.R.O.) to identify pulmonary infiltrates. The mean ratio of PaO₂ to the fraction of inspired oxygen (FiO₂) was recorded in the first 24 h after the lung transplantation. PRR was diagnosed when the following criteria were present within the first 24 h of transplant: (1) allograft infiltrates on chest radiographs, (2) hypoxemia with FiO₂ ≥ 0.30 to maintain arterial oxygen tension ≥ 65 mm Hg, (3) pulmonary artery occlusion pressure ≤ 12 mm Hg, and (4) absence of infection and rejection. Chest radiographs showing lung infiltrates after 24 h of lung transplantation were not categorized as PRR.

Severity of lung infiltrates on chest radiographs was graded using a categorical scale from 0 (none) to 5 (severe) as shown in Table 1. Lungs on the chest radiograph were divided into three zones. Area of the lung above the aortic arch was labeled as upper zone, area of the lung below the pulmonary veins as lower zone, and the area of the lung between upper and lower zones was labeled as middle zone. The severity of PRR on chest radiographs increased with the number of zones involved.

The following potential clinical predictors of PRR were evaluated: age and sex of recipient, underlying lung disease, allograft ischemia time, type of transplant (single-lung vs double), use of cardiopulmonary bypass during surgery, and the presence of preoperative pulmonary hypertension.

Statistical Analysis

Univariate analysis was performed to test for association between PRR and potential baseline risk factors (age, sex, underlying diagnosis, type and side of transplant, and cardiopulmonary bypass), hospital outcome variables (ICU stay, duration of mechanical ventilation and length of hospital stay, ischemia time, and mean PAP), and long-term survival. A two-sided t test was used for comparing the PRR and no PRR groups on continuous variables, Wilcoxon rank-sum test for ordinal variables, and a test for categorical variables. Correlation between PRR grade 0 to 5 and either continuous or ordinal variables was assessed with Spearman correlation coefficient. The association of baseline categorical factors with severity of PRR was assessed with Wilcoxon rank-sum test or Kruskal-Wallis test. Baseline predictors of long-term survival in these patients were assessed with Kaplan-Meier curves or Cox proportional hazards regression models and log-rank tests.

Identification of PRR

There were 99 patients who underwent lung transplantation at The Cleveland Clinic Foundation between February 1990 and October 1995. The mean age of recipients was 43 years (range, 11 to 62 years). Fifty patients were men and 49 were women. Sixty-four patients received a single lung (left lung, 41 patients; right lung, 23 patients), whereas bilateral sequential lung transplantation was performed in 35 patients. The indications for transplantation included emphysema (n = 41), CF (n = 21), idiopathic pulmonary fibrosis (IPF) (n = 11), and PPH (n = 9). Other indications included lymphangioleiomymatosis (n = 2), systemic lupus erythematosus with lung fibrosis (n = 2), sarcoidosis (n = 2), bronchiectasis (n = 2), pulmonary hemosiderosis (n = 1), hypocomplementemic urticarial vasculitis syndrome (n = 1), obliterative bronchiolitis (n = 1) and secondary pulmonary hypertension (n = 6) from atrial septal defect (n = 4), ventricular septal defect (n = 1), and patent ductus arteriosus (n = 1).

The mean allograft ischemia time was 236 min (range, 164 to 458 min) for double-lung transplant and 168 min (range, 80 to 358 min) for single-lung transplant. Thirty-seven (37%) patients required cardiopulmonary bypass during the surgery. The median time on cardiopulmonary bypass was 105 min (range, 46 to 198 min).

Prevalence of PRR by Risk Factors

Overall, 56 of 99 recipients (57%) experienced PRR after lung transplantation. The mean PaO₂/FiO₂ ratio in these patients was significantly lower in the first 24 h after transplant than in patients who did not have PRR (254 ± 110 vs 404 ± 137; p < 0.001).

The mean age of patients with PRR was similar to those who did not have PRR (44 ± 13 years vs 41 ± 14 years; p = 0.43; Table 2). Twenty-eight of 50 men (56%) and 28 of 49 women (57%) experienced PRR. Thus, no association was found between sex and development of PRR (p = 0.91).

Twenty-five of 41 patients (61%) with emphysema, 8 of 11 patients (73%) with IPF, 12 of 21 patients (57%) with CF, and 5 of 9 patients (55%) with PPH experienced PRR (Fig 1). Six of the 17 remaining patients (35%) had PRR. Although IPF patients had a slightly higher incidence of PRR, there was no evidence that any underlying lung disease was a risk factor (p = 0.32).

Eighteen of 35 double-lung transplant recipients (51%), 26 of 41 left lung transplant recipients (63%), and 12 of 23 right lung transplant recipients (52%) experienced PRR. Side or type (double lung vs single lung) did not predict PRR (p = 0.51; Table 2).

Allograft ischemia time did not predict PRR. The
median ischemia time of patients with PRR was 168 min compared with 180 min for those patients who did not have PRR (p = 0.62). The maximal allograft ischemia time was 458 min.

Sixty of the 99 patients underwent preoperative right heart catheterization. Thirty of these 60 patients had normal PAP (mean, 25 mm Hg). Eighteen patients had mild to moderate pulmonary hypertension (mean PAP, 25 to 50 mm Hg), and 12 had severe pulmonary hypertension (mean PAP, > 50 mm Hg). The incidence of PRR was 51% in patients without pulmonary hypertension, 78% in the mild to moderate group, and 58% in patients with severe pulmonary hypertension. The differences among the three groups were not significant (p = 0.10).

Thirty-seven patients required cardiopulmonary bypass during surgery. The mean time on cardiopulmonary bypass (pump time) was 109 min (quartiles, 71, 141 min). Patients who required cardiopulmonary bypass during surgery (26 of 37 patients; 70%) had significantly higher rate of PRR compared with those who did not (30 of 62 patients; 48%; p = 0.03; Table 2).

**Severity Grade of PRR by Risk Factors**

Chest radiographs of patients who experienced PRR after lung transplantation were graded on a severity scale of 0 (none) to 5 (very severe; Table 1). As shown in Table 3, patients with higher PRR grade had lower PaO₂/FIO₂ ratio (p < 0.001). In this study, ischemia time of the allograft did not predict the degree of PRR (Table 3). Similarly, underlying lung disease, age, or sex of the recipient as well as type or side of transplant did not correlate with the severity of the PRR. However, patients who required cardiopulmonary bypass during surgery had significantly higher grade of PRR on chest radiograph or arterial blood gas abnormalities compared with those who did not (median severity grade, 2.0 vs 0.5; Wilcoxon rank sum test, p = 0.01; Fig 2). The duration of pump time did not correlate with the severity of PRR.

**Outcome Measures**

The median (quartiles) duration of stay in the ICU of patients who had PRR was 8 (5, 20) days compared with 6 (5, 10) days for those without PRR (p = 0.03). Patients who had PRR also required longer duration of mechanical ventilation (median (quartiles), 3 [2, 7] days vs 2 [1, 3] days; p = 0.009). However, overall length of stay in the hospital of patients with and without PRR was not significantly different (median (quartiles), 24 [18, 39] days vs 21 [15, 27] days; p = 0.08; Table 4). Duration of ICU and hospital stay correlated positively with the severity of PRR, and patients with a higher grade of PRR also required longer duration of mechanical ventilation (p < 0.001; Table 3).

A total of 20 of 99 lung transplant recipients died postoperatively. The underlying diagnoses in these patients were PPH (n = 4), emphysema (n = 5), CF (n = 4), IPF (n = 3), sarcoidosis (n = 1), Eisenmenger’s secondary to atrial septal defect (n = 1) and ventricular septal defect (n = 1), and systemic lupus erythematosus with pulmonary fibrosis (n = 1). The cause of death for seven of these patients was infection (two cases of candida sepsis, two of invasive aspergillosis, two of cytomegalovirus infection, and one of *Pseudomonas aeruginosa* pneumonia). Four patients died from pulmonary embo-
Three from acute allograft rejection, three from severe PRR response, and one patient died of necrosis of bronchial anastomosis and dehiscence of the bronchus. The remaining 2 of these 20 patients died intraoperatively. Fourteen of the 20 patients died in the ICU, 11 while still being ventilated. The remaining 9 of the 20 patients were not on a ventilator at the time of their death (acute pulmonary embolism in 4 patients, intraoperative deaths in 2 patients, invasive aspergillosis in 1 patient, cytomegalovirus infection in 1 patient, and necrosis of bronchial anastomosis in 1 patient). A total of 12 of these 20 patients had PRR in the immediate postoperative period whereas 8 patients did not have PRR. Only 3 of these 12 patients died of severe PRR. However, six of the remaining nine patients were successfully extubated after improvement in PRR and died of causes unrelated to PRR. Similarly, the remaining three patients with PRR who were ventilated until their death also died of other complications unrelated to PRR (acute pulmonary embolism in one patient, invasive aspergillosis in one patient, and pseudomonas infection in one patient).

Of the patients who were discharged from the hospital (n = 79) after the surgery, the mean follow-up time was 52 months (range, 30 to 90 months). The overall median Kaplan-Meier survival of patients (including postoperative deaths) was 34 months (range, 0 to 90 months).

Survival of female lung transplant recipients was significantly better than that of male recipients (median survival, 60 months vs 21 months; p = 0.02; Fig 3). The median survival of patients who had PRR was 28 months compared with 36 months for patients who did not have PRR (p = 0.99; Fig 4). Thirty-day survival of patients who experienced PRR was 86% (95% confidence interval [CI], 77 to 95%) compared with 84% (95% CI, 73 to 95%) in patients without PRR. Thus, PRR also did not affect the long-term survival of the patients. One-year survival was 68% (95% CI, 56 to 80%) in patients with PRR compared with 65% (95% CI, 51 to 79%) in patients without PRR. Similarly, 3-year survival was also similar in the two groups (49% vs 48%).

**Discussion**

The PRR consists of morphologic, functional, and roentgenographic changes that occur in the allograft in the early posttransplantation period. Clinically, it presents as hypoxemia and pulmonary infiltrates in the allograft in the first 24 h after transplantation. PRR is a diagnosis of exclusion, and other causes of hypoxemia and lung infiltrates such as rejection, infection, and cardiogenic pulmonary edema need to be excluded. The diagnosis of PRR is usually made by the following criteria that are met in the first 24 h after transplant: (1) chest radiograph showing alveolar and or interstitial infiltrates, (2) pulmonary artery occlusion pressure ≤ 12 mm Hg, (3) hypox-
emia (FiO₂ ≥ 0.30 to maintain arterial oxygen tension of 65 mm Hg), and (4) no evidence of infection or rejection. In addition to arterial hypoxemia, PRR may be associated with systemic hypotension and a reduction of cardiac output. The pathogenesis of PRR is not fully understood; however, various cytokines and the generation of free oxygen radicals during reperfusion of the allograft have been implicated in its causation. Both ischemia and reperfusion seem to be essential to the development of PRR. Although PRR has been extensively investigated in animal models, only limited data is available in human lung transplant recipients.

Parenchymal infiltrates in the allograft consistent with PRR are a radiologic finding in the first 24 h of the postoperative period. Herman reported this process in 13 of 14 single-lung transplant recipients. In another study, 24 of 40 single-lung transplant recipients (60%) had PRR. PRR begins in the first 24 h after lung transplantation and generally worsens over time, reaching its peak in 4 to 7 days. In this study, 56 of 99 patients (57%) demonstrated infiltrates on chest radiographs within 24 h after transplantation, along with arterial hypoxemia. When lung infiltrates and hypoxemia developed after 24 h, fluid overload, infection, or allograft rejection were the usual causes. In our patients, we excluded infection by regular cultures of tracheal aspirate, blood cultures, BAL, and protected brush specimens. Because allograft rejection is uncommon in the first 24 h of lung transplantation, transbronchial biopsies were performed in patients who had lung infiltrates after the first 24 h at the discretion of the transplant physician.

Which lung transplant recipients are susceptible to PRR is not clearly known. Earlier reports suggest that prolonged allograft ischemia time predisposes to PRR. Sleiman et al studied 40 patients who received single-lung transplants and found that the mean ischemia time of patients with PRR was higher (241 ± 103 min) than patients who did not have PRR (155 ± 71 min). Other studies have suggested that an ischemia time of up to 6 h does not result in clinical dysfunction of the allograft. The ischemia time in our patients was much shorter than in other studies, but similar to the ischemia time reported recently by Christie et al. The median ischemia time was 168 min (quartiles, 142, 211 min) in patients with PRR and 180 min (quartiles, 150, 221 min) without PRR, with the longest ischemia time being 458 min. Thus, we believe that the relatively short ischemia time in our study resulted in failure to identify ischemia time as a risk factor for PRR.

*Wilcoxon rank sum test.
†Patients not surviving the interval are excluded.

Figure 3. Kaplan-Meier survival analysis of male and female lung transplant recipients. Survival of female lung transplant recipients was significantly better than that of male lung transplant recipients (p = 0.02).

Figure 4. Kaplan-Meier survival analysis of lung transplant recipients with and without PRR. Overall survival in lung transplant recipients who experienced PRR was similar to those who did not have PRR (p = 0.99).
PRR probably results from increased capillary permeability of the lung microcirculation. In single-lung transplant recipients with pulmonary hypertension, the majority of the pulmonary artery blood flow is directed toward the allograft because of the lower vascular resistance. Hence, patients with pulmonary hypertension are expected to have more severe degree of PRR. Bando et al reported 63% incidence of PRR in patients with pulmonary hypertension (12 of 19 patients), which is similar to the incidence in this study (56%). Kawaguchi et al have shown that, in a rat model, severity of PRR depends on severity of pulmonary hypertension. In this study, PRR developed in 51% of patients without pulmonary hypertension, 78% of patients with mild to moderate pulmonary hypertension, and 58% of patients with severe pulmonary hypertension (p = 0.10). Among those who underwent right heart catheterization (n = 60), the mean PAP was 32 ± 17 mm Hg in patients with PRR and 33 ± 16 mm Hg in patients who did not have PRR (p = 0.28). Moreover, the incidence of PRR in double-lung transplant recipients was similar to that of single-lung transplant recipients, suggesting that double-lung transplantation was not better than single-lung transplantation in preventing PRR.

Some patients require cardiopulmonary bypass during lung transplantation. The general recommendation is that cardiopulmonary bypass should be avoided during lung transplant because it adds technical complexity to the procedure and increases ischemia time by prolonging operative time. Cardiopulmonary bypass also induces cytokine production (interleukin [IL]-1, IL-6, IL-8, tumor necrosis factor, and interferon-γ), probably in part because of contact of the blood with the pump membrane. Some of these cytokines may increase lung capillary permeability and have been implicated in ischemia-reperfusion injury after lung transplantation. Some clinical studies have suggested that patients requiring cardiopulmonary bypass during lung transplantation may have a greater degree of allograft dysfunction and an increased alveolar-arterial oxygen difference. In this study, the incidence of PRR was higher in patients who underwent cardiopulmonary bypass compared with those who did not (70% vs 48%; p = 0.03). Moreover, patients who underwent cardiopulmonary bypass had a higher grade of PRR compared with those who did not undergo cardiopulmonary bypass (Fig 2).

Finally, we analyzed the data to determine whether the underlying lung disease was associated with the severity of PRR. Patients with IPF had a slightly higher incidence and severity of PRR compared with patients with other diseases, but the difference was not statistically significant. Interestingly, patients with PPH did not have a more severe degree of PRR.

Patients who experienced PRR required longer duration of mechanical ventilation and required additional days of ICU stay compared with patients who did not have PRR. Overall, the hospital stay of patients with and without PRR was not different. However, in patients who survived the surgery and were discharged from the hospital, the number of hospital days correlated with the severity of PRR (p = 0.006; Spearman correlation; Table 3). Moreover, patients with a higher grade of PRR had an increased duration of mechanical ventilation (p < 0.001) and required more days in the ICU (p = 0.001). Despite prolonging the ICU stay, PRR had no impact on 30-day survival.

**CONCLUSION**

PRR developed in 57% of 99 patients undergoing lung transplantation. Most patients have a mild to moderate degree of PRR. The development of PRR was not associated with prolonged ischemia time, preoperative pulmonary hypertension, type of lung transplant, underlying lung disease, or age or sex of the recipients. However, the use of cardiopulmonary bypass during surgery increased the risk and severity of PRR. Compared with men, female lung transplant recipients had significantly better survival. Patients with PRR required prolonged mechanical ventilation and had a longer ICU stay, although PRR did not affect 1- or 3-year survival.

**REFERENCES**

12 Weill D, Zamora MR. Postoperative care in lung transplantation. Semin Respir Crit Care Med 1996; 17:159–166