

## Review Article

# Long Term Impact of Primary Graft Dysfunction after Lung Transplantation

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Submitted: 08 December 2014

Accepted: 08 February 2015

Published: 10 February 2015

ISSN: 2333-6625

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**Abstract**

Primary graft dysfunction (PGD) is a common early complication after lung transplantation and represents an acute lung injury with clinical, radiographic, and histological features similar to acute respiratory distress syndrome (ARDS). PGD is associated with prolonged mechanical ventilation, longer intensive care unit and hospital stays, and increased short-term mortality. Importantly, recipients who develop severe PGD are at increased risk of long-term mortality and may have worse functional status and lower peak lung function. In addition, all grades of PGD are associated with an increased risk of chronic rejection. Multiple donor and recipient factors have been linked with the development of PGD, and therapy consists primarily of supportive care similar to patients with ARDS.

**INTRODUCTION**

According to the International Society for Heart and Lung Transplantation (ISHLT) Registry, graft failure accounted for 24.7% of deaths within 30 days of transplantation among adult lung recipients between 1992 and 2012 [1]. Although important details distinguishing different causes of early graft failure may be missing from the Registry data, it is likely that primary graft dysfunction (PGD) is the leading cause of early graft failure. PGD was initially described in 1973 when autologous lung re-implantation in canines was associated with functional defects in the early post-operative period even when re-implantation was "technically flawless." Serial radiographs after re-implantation and biopsy specimens demonstrated pulmonary edema despite normal pulmonary angiograms [2]. These findings led investigators to suspect ischemia followed by reperfusion as the cause of this graft injury. Forty years later, the predominant explanation for the mechanism of tissue damage characteristic of PGD still underscores the role of ischemia-reperfusion injury [3,4]. This early injury after lung transplantation is thought to include an acute phase, involving macrophage-mediated microvascular endothelial damage, and a delayed phase, mediated by neutrophil and monocyte graft infiltration [5]. Nonetheless, it is likely that PGD represents the end-result of multiple insults that begin with donor brain death and possible neurogenic pulmonary edema, aspiration, and ventilator-induced lung injury followed by ischemia when the donor organ is retrieved and reperfusion at the time of implantation.

PGD is characterized clinically and radiographically by hypoxemia and pulmonary edema occurring in the first 72 hours after transplantation [4]. Histologically, PGD manifests as an acute lung injury that is characterized by diffuse alveolar damage in its most severe form. There is a spectrum of severity varying from mild abnormalities in pulmonary function to severe hypoxemic respiratory failure requiring intensive support. Fortunately, a minority of lung transplant recipients develops severe PGD while others have mild or moderate impairment in pulmonary function. The majority of recipients improve over time with supportive care, but some patients have progressive or persistently severe graft dysfunction and ultimately die or require re-transplantation. However, survivors who appear to recover completely from the acute injury have worse long-term outcomes than recipients who did not develop PGD. This manuscript will review the clinical presentation and management of PGD and focus on its impact on long-term outcomes after lung transplantation.

**CLINICAL, RADIOLOGIC AND PATHOLOGIC DIAGNOSIS**

Hypoxemia and radiographic infiltrates are the characteristic findings of graft dysfunction in the immediate period after lung transplantation. Determining the cause of graft dysfunction early after lung transplantation can be difficult. The differential diagnosis includes hyper acute rejection, donor-imported lung injury, venous anastomotic complications, pneumonia, and PGD. Donor radiographs are reviewed prior to acceptance to evaluate for signs of acute lung injury, which may render

them less optimal candidates for lung donation. Further, the circumstances that lead to organ donation frequently predispose to aspiration, pneumonia or contusion, all of which may persist after transplantation. Transfusion of blood products in the intra operative and postoperative period may lead to transfusion associated lung injury, which is radiographically similar to PGD. Finally, excessive fluids given for perioperative hypotension may lead to the development of hydrostatic pulmonary edema, which confounds the diagnosis. These possibilities are all considered in the evaluation of early post-transplant graft dysfunction.

Patients with PGD exhibit a pattern of radiographic infiltrates consistent with pulmonary edema as seen in ARDS. Similarly, the characteristic pathology of PGD is acute lung injury with diffuse alveolar damage in its most severe form [4]. Diffuse alveolar damage is a pathologic finding of diffuse, temporally homogenous septal thickening with airspace organization and hyaline membrane deposition in the absence of prominent eosinophilia, neutrophilia, and viral inclusions [6]. Diffuse alveolar damage is a non-specific pathology representing severe acute and organizing lung injury, and can be seen in various clinical settings including ARDS complicating septic shock, pneumonia, drug-induced pneumonitis, and exacerbations of pulmonary fibrosis [7]

In a retrospective review of biopsies obtained within 1 week of lung transplantation, 55 of 291 (19%) patients had evidence of diffuse alveolar damage [8]. In a separate series, 37% of patients had diffuse alveolar damage on biopsies taken up to 3 months after lung transplantation [9]. Many of these biopsies were taken as part of routine surveillance for acute rejection protocols and neither series outlined the incidence of PGD although these studies underscore the frequency of acute lung injury early after transplantation.

## DEFINITION

As the number of lung transplants performed worldwide increased through the 1990s, investigators began to describe a growing experience with a syndrome of unexpected early graft dysfunction. One center described diffuse alveolar infiltrates on radiography with a ratio of  $\text{PaO}_2$  to  $\text{FiO}_2$  (PF ratio)  $< 200$  beyond 48 hours after transplantation and continued ventilator dependence beyond 5 days in the absence of a clear cause of graft dysfunction. In a series of 100 patients, this occurred in 15% and resulted in longer post-operative hospitalizations and increased one-year mortality [10]

Using a less restrictive definition, Khan and colleagues described a syndrome of hypoxemia ( $\text{FiO}_2 \geq 0.3$  to maintain arterial oxygen tension  $\geq 65$  mmHg) and radiographic infiltrates in the absence of infection, rejection, and elevated pulmonary artery occlusion pressures. Using this definition, 57% of lung transplant recipients developed early graft dysfunction associated with prolonged mechanical ventilation and ICU stay. However, survival was not affected up to 72 months after transplantation [11]. Several other centers reported similar data with incidences and outcomes varying according to the definition used for case identification.

Recognizing the importance of this problem and the difficulty in unifying research across centers absent a cogent definition, the ISHLT chartered a working group on PGD in 2004. This group

adopted a time-based classification scheme and a definition based on radiographic infiltrates consistent with pulmonary edema and impairment in the  $\text{PaO}_2$  to  $\text{FiO}_2$  (PF) ratio. According to this definition, recipients who do not have radiographic pulmonary edema are graded PGD 0 (or no PGD) while those with radiographic pulmonary edema are graded PGD 1 if the PF ratio is  $>300$ , PGD 2 if the PF ratio = 200-300, and PGD 3 if the PF ratio is  $< 200$ . Recipients requiring extracorporeal membrane oxygenation (ECMO) after transplantation are graded PGD 3 [4]. Since the severity of the acute lung injury can change over a short period of time, grading is done immediately after transplantation (T0), at 24 hours (T24), at 48 hours (T48), and at 72 hours (T72). Finally, implicit in this definition is the exclusion of other potential causes of early graft dysfunction including hyper acute rejection, vascular anastomotic complications, cardiogenic pulmonary edema, and pneumonia.

## INCIDENCE

Using this definition, the incidence of PGD 0 was 19%, PGD 1 39%, PGD 2 21%, and PGD 3 21% immediately after transplantation in a retrospective single-center study [12] Similarly, the incidence of PGD was evaluated in a multicenter cohort study across 10 centers in the United States; among 1,255 patients, 211 (16.8%) developed PGD 3 by 72 hours post-transplant [13]. These incidences are consistent with previously reported rates of PGD, which have ranged from 10-25%, though many studies have included patients identified before the era of the consensus definition [14]

## RISK FACTORS

Early analyses of patients with PGD described an increased incidence among patients with longer cold graft ischemic time [15]. Additional data suggested that patients transplanted for pulmonary hypertension were at an increased risk of PGD [16]. Both of these observations correlated with the prevailing paradigm that graft dysfunction after lung transplantation was at least in part due to cold ischemia followed by reperfusion. Subsequent analyses identified donor variables including female gender, African American race, and age  $<21$  or  $>45$  years as significant risk factors for PGD within 72 hours of transplantation [17]. A 2006 review of data from the ISHLT Registry demonstrated that pre-operative recipient diagnosis, increased recipient pulmonary artery pressure, donor smoking history  $> 10$  pack-years, older donor age and transplantation between 1992 and 1998 (as compared to the more recent era) were associated with an increased incidence of PGD 3 [18]. Interestingly, graft ischemic time was not associated with an increased incidence of PGD in this analysis. In another series of over 1200 patients transplanted between 2002 and 2010, recipient body mass index, elevated  $\text{FiO}_2$  during graft reperfusion, use of cardiopulmonary bypass, and recipient diagnoses of sarcoidosis or pulmonary hypertension were identified as significant risk factors for PGD 3 [13]. Again, graft ischemic time was not associated with a significantly increased risk of PGD in this series. A systematic review and meta-analysis of 13 studies from 1970 to 2013 validated pre-transplant diagnoses of sarcoidosis or pulmonary hypertension, recipient obesity and use of cardiopulmonary bypass during transplantation as risk factors for primary graft dysfunction [14]. This series also identified recipient female

gender, African American race, and diagnosis of idiopathic pulmonary fibrosis as significant risk factors for PGD.

Using latent class analysis, a statistical model designed to define groups of subjects based on shared observations, the Lung Transplant Outcomes Group cohort was examined to identify classes of patients with PGD; 361 patients in the cohort developed PGD 3 within 72 hours of transplantation. Patients were grouped into classes that sustained either severe persistent dysfunction, completely resolved, or improved without complete resolution within 72 hours. Those without resolution of PGD had significantly higher mortality and were more likely to have received blood product transfusions, required cardiopulmonary bypass intra-operatively, or carried a diagnosis of pulmonary arterial hypertension prior to transplantation [19]. These data raise the possibility of a distinct subgroup of patients with severe PGD and identify potentially modifiable risk factors.

Much of the evolving effort to decrease rates of PGD will depend on optimization of donor characteristics. Early studies demonstrated an increased risk of PGD in the setting of receiving lungs from a donor who is <21 or >45 years of age [17]. This finding, however, has not been validated in more modern series [13]. Shigemura and colleagues demonstrated that patients who received lung transplants from donors >55 years of age had significantly lower peak FEV<sub>1</sub> measurements than patients from younger donors (71.7% predicted vs. 80.7% predicted, respectively). However, the use of older donors was not associated with an increased risk PGD or early mortality [20].

In contrast, donor smoking has consistently been associated with an increased risk of PGD. In one series, recipients of transplants from donors with any history of smoking had a nearly two-fold increased risk of PGD [13]. Similarly, out of 1,295 lung transplants done in the United Kingdom, 510 (39%) were obtained from donors with a smoking history. In this large cohort, donor smoking was associated with a significantly worse 3-year mortality compared to those whose donors never smoked [21]. Furthermore, recipients from donors who smoked had significantly lower FEV<sub>1</sub> measurements than recipients of nonsmoking donors. However, despite the increased mortality associated with smoking donors, there was a significantly better 3-year survival among transplant recipients of smoking donors compared to listed patients who did not have a transplant during this time period [21]. This finding is compelling evidence that despite the increased risk of PGD and early mortality associated with smoking donors; the exclusion of such donors from the donor pool would further restrict access to transplantation for patients with end-stage lung disease and increase wait-list mortality.

Many centers use extended-criteria donors to expand the donor pool. Zych and colleagues compared 79 patients who received transplants from extended-criteria donors (i.e., those with a PF ratio <300, age over 55 years, and a history of smoking >20 pack-years) to 169 recipients of ideal donors. There were no significant differences in the incidence of PGD, length of stay, rejection, or mortality between recipients of extended-criteria donors and ideal donor recipients [22]. While these findings contrast with much of the literature surrounding risk factors for PGD, the data suggest that carefully selected extended-criteria

donors may have comparable outcomes to ideal donors. This also raises interesting questions about the mechanistic link between these risk factors and the development of PGD. Additionally, donation after cardiac death (DCD) has been demonstrated to be a viable option for expanding the donor pool. In a series of 72 transplants from DCD donors, the incidence of PGD was 8%, which is similar to the incidence of PGD after transplantation from brain-dead donors [23]. In addition; DCD donor recipients had a significantly better 5-year survival than brain-dead donor recipients. Finally, *ex vivo* lung perfusion (EVLV) has been reported as a treatment to optimize donor lungs prior to transplantation. Evidence suggests that EVLV treatment can improve the quality of donor lungs that were initially rejected such that they can be safely transplanted with good outcomes [24,25]. Indeed, intermediate-term outcomes, including the incidence of PGD, after transplantation using donor lungs treated with EVLV are comparable to conventional donor transplants [26,27]

## MANAGEMENT

Given the similarities between PGD and ARDS, most treatment standards have focused on supportive care until recovery from the underlying injury. In one center, implementation of a tightly controlled ventilator and hemodynamic management protocol resulted in significant reductions in severity of PGD [28]. Beyond that, low tidal volume ventilation, careful attention to intravascular volume, and other strategies for the management of acute lung injury have been standard in the support of patients with PGD. For carefully selected patients with persistent severe PGD, re-transplantation may be an option, but poor outcomes and emergent donor availability limit a more widespread use of this approach [4]. Until additional data regarding optimal treatment strategies emerge, general supportive measures remain the only available option for patients with PGD.

## IMPACT OF PGD ON MORTALITY

Not surprisingly, severe PGD is associated with increased mortality after transplantation. In a series of biopsies from 720 lung transplant recipients, diffuse alveolar damage (the characteristic pathology of severe PGD) was identified in 264 patient biopsies within the first three months of transplantation. This finding was associated with a significantly higher risk of 90-day mortality [29]. This correlated with the clinical diagnosis of PGD in the cohort from the Lung Transplant Outcomes Group, in which PGD 3 was associated with absolute risk increases of 18% and 23% for 90-day and 1-year mortality, respectively, when compared with patients who did not develop PGD [13]. Indeed, in the era prior to the consensus definition of PGD, a formal review of the ISHLT database demonstrated a mortality rate of 42.1% among patients who had a PaO<sub>2</sub>/FiO<sub>2</sub> ratio <200 beyond 48 hours after transplantation with radiographic infiltrates and the absence of a clear cause [4]. This was significantly higher than patients without PGD. Importantly, mortality among patients who developed PGD and survived at least one year after transplantation was still significantly worse than those who did not develop PGD suggesting that the early graft injury affected outcomes beyond the immediate period after transplantation [4]. Since chronic lung allograft dysfunction (CLAD) is the leading cause of death beyond the first year after transplantation,

multiple studies have investigated the potential association between PGD and the subsequent development of CLAD and bronchiolitis obliterans syndrome (BOS) [12,30].

## IMPACT OF PGD ON CHRONIC LUNG ALLOGRAFT DYSFUNCTION

In addition to increased mortality, patients with PGD often have significant functional impairments throughout the life of their graft. Among 100 consecutive lung transplant recipients, 15% developed early graft dysfunction, and these patients had a median ventilator dependence of 36 ( $\pm$ 43) days, which was significantly longer than the 4 ( $\pm$ 6) days among patients without early dysfunction [10]. A larger scale review validated this finding among 255 recipients. In this series, patients with PGD were significantly more likely to have prolonged durations of mechanical ventilation with median ventilator requirements of 15 days compared to 1 day among patients without PGD. This was associated with a median hospital length of stay of 47 days among patients with PGD and 15 days among those without PGD [4]. Furthermore, patients with PGD have significantly longer times to normalization of 6 minute walk distance and significant decreases in the forced expiratory volume in 1 second (FEV<sub>1</sub>) which persists throughout their lives [4,10,30].

Given the poor long-term outcomes seen among patients with PGD, investigators hypothesized that PGD would be associated with an increased risk of chronic allograft rejection, or BOS. To investigate this potential association, records from 134 patients transplanted between 1990 and 2000 were reviewed; 34% of those who developed hypoxemia and radiographic evidence of lung injury within 24 hours of transplantation went on to develop BOS compared with 12% of those who did not experience this early graft dysfunction. In addition, patients with PGD had an increased risk of developing progressive stages of BOS [29]. In a single-center retrospective study, long-term outcomes after PGD, as defined by ISHLT criteria, were assessed in 334 adult lung transplant recipients. Across all grades, patients with PGD were found to have a significantly increased risk of BOS. The relative risks of this association were 1.73, 2.13 and 2.53 for PGD1, 2 and 3, respectively [12]. Importantly, this association was independent of other recognized risk factors for BOS including acute rejection, lymphocytic bronchiolitis, and community associated respiratory viral infections. Furthermore, data from the same cohort suggest that improvement in PGD grade over the first 72 hours is associated with a lower risk of BOS while worsening PGD grade over this time period is associated with an increased risk of BOS [31]. However, the exact mechanism that the early acute lung injury of PGD increases the risk of BOS months or years later remains uncertain.

Over the past 15 years, the development of donor-specific human leukocyte antigen (HLA) antibodies (DSA) has been increasingly recognized as an important risk factor for BOS [32-35]. Additionally, post-transplant graft injury is thought to up-regulate HLA expression in the graft, which can lead to the development of allo-immunity and HLA antibodies. Based on this, investigators used flow cytometry and interferon gamma release assays to assess a series of cytokines and DSA in patients who developed PGD. Recipients with PGD 1-3 were significantly more

likely to develop class II DSA and had higher concentrations of multiple pro-inflammatory cytokines, which up-regulate the expression of class II HLA in the graft (MCP-1, IP-10, interleukin (IL) 1- $\beta$ , IL-2, interferon- $\gamma$  and IL-12) [36]. Additionally, 52.2% of patients with PGD developed *de novo* donor-specific HLA antibodies after transplantation compared to 13.5% of those without PGD. These findings suggest that PGD promotes donor-specific alloimmune responses, which subsequently increase the risk of BOS development. Furthermore, the acute lung injury and subsequent remodeling associated with PGD may expose sequestered lung restricted self-antigens such as collagen V and K- $\alpha$  1 tubulin [37-40]. Loss of peripheral tolerance can then propagate cellular and humoral immune responses to these self-antigens and promote the development of graft rejection [38,39,41,42]. Furthermore, the epithelial cell injury characteristic of PGD may serve as the necessary "danger signal" that activates the recipient's alloimmune response [43,44]. Lastly, non-alloimmune mediated airway remodeling after PGD may lead to BOS.

Recently, a restrictive phenotype of CLAD has been increasingly recognized. Among patients who develop CLAD, a subgroup develops progressive diminution of forced vital capacity (FVC) and total lung capacity (TLC). This newly described entity has been called the restrictive allograft syndrome (RAS) and is pathologically associated with diffuse alveolar damage that may progress to pleuroparenchymal fibroelastosis [45,46]. No series has yet examined the relationship between early PGD and this chronic restrictive CLAD though these histopathologic findings may suggest a pathophysiologic relationship.

## CONCLUSION

PGD represents a serious challenge in the care of lung transplant recipients. Obesity, pre-transplant diagnosis of pulmonary hypertension or sarcoidosis, a donor history of smoking, and the need for cardiopulmonary bypass have consistently been identified as significant risk factors for PGD. Severe PGD increases the risk of mortality in the early period after transplantation. Beyond this, PGD is associated with an increased risk of CLAD and persistent functional impairment after initial recovery from transplantation. While more conservative donor selection may mitigate the risk of PGD, this would narrow the donor pool and may increase waitlist mortality. Finally, *ex vivo* lung perfusion is a viable option for pre-operative conditioning of donor lungs to expand the donor pool. While this has not yet shown a decrease in the incidence of PGD, larger studies will be necessary to address this question. Once PGD has developed, supportive measures similar to those used in the management of ARDS are generally employed until recovery. In summary, PGD remains a persistent challenge affecting immediate and long-term outcomes after lung transplantation, and additional studies are needed to further delineate modifiable risk factors and improve outcomes.

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#### Cite this article

Aguilar PR, Hachem R (2015) Long Term Impact of Primary Graft Dysfunction after Lung Transplantation. *Clin Res Pulmonol* 3(1): 1026.