Primary Graft Dysfunction After Lung Transplantation

Mary K. Porteous, MD, MSCE[a,b,*], James C. Lee, MD[a]

KEYWORDS

• Primary graft dysfunction • Ischemia-reperfusion injury • Lung transplantation • Acute lung injury

KEY POINTS

- Primary graft dysfunction following lung transplantation remains a significant source of short- and long-term morbidity and mortality.
- Primary graft dysfunction represents the end result of multiple deleterious mechanisms provoked by donor brain death, mechanical ventilation, procurement, storage, and ischemia reperfusion injury.
- Improved understanding of the role of genetic and clinical risk factors and the mechanisms underlying primary graft dysfunction will identify potential high-risk populations and therapeutic targets for future study.
- Extracorporeal life support offers promise to develop and administer new therapeutic agents for primary graft dysfunction and to potentially safely expand the donor pool without increasing the risk of primary graft dysfunction.

INTRODUCTION

Primary graft dysfunction (PGD) is a form of acute lung injury following lung transplantation associated with significant morbidity and mortality.[1–7] This article reviews the epidemiology, pathogenesis, risk factors, prevention, and treatment of PGD.

EVOLUTION OF THE DEFINITION OF PRIMARY GRAFT DYSFUNCTION

PGD is characterized by hypoxemia and alveolar infiltrates in the allograft consistent with edema that develops within 72 hours of lung transplantation.[2] Early case reports referred to postoperative allograft dysfunction by various terms, including reimplantation edema or response, reperfusion injury, and primary graft failure.[4,8–12] The criteria used by individual centers to describe early allograft dysfunction were equally as varied. Although most classification schemes used the ratio of partial pressure of arterial oxygen (Pa_{O_2}) to fraction of inspired oxygen (Fi_{O_2}) (P/F), the cutoff P/F and the amount of positive end-expiratory pressure (PEEP) used during P/F measurements differed. Exclusion of other causes of infiltrates, including infection, rejection, and cardiogenic edema, were recommended, but the methodology varied.[8,10–14] Only a few case series required documentation of a pulmonary artery occlusion pressure (PAOP) of less than 12 to 18 mm Hg in order to exclude cardiogenic edema,[10,13] possibly because of the inaccuracy of measuring PAOP while on mechanical

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[a] Department of Medicine, Perelman School of Medicine, University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104, USA; [b] Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, 423 Guardian Drive, Philadelphia, PA 19104, USA
* Corresponding author. 839 West Gates, 3400 Spruce Street, Philadelphia, PA 19104.
E-mail address: mary.porteous@uphs.upenn.edu

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ventilation or because of the potential for hazardous complications while measuring PAOP in post–lung transplant patients.[8,15,16] Inconsistent criteria for PGD, therefore, contributed to variability in reported incidences and risk factors.

In 2005, the International Society for Heart and Lung Transplantation (ISHLT) generated a classification system that aimed to standardize the definition of PGD to facilitate mechanistic and clinical trials.[2] PGD is now graded from 0 to 3 based on P/F and the presence of radiographic infiltrates consistent with pulmonary edema (**Table 1**). Grade 3 PGD (PGD3) corresponds to a P/F of less than 200 with allograft infiltrates. Exclusion of contributing factors, including hyperacute rejection, pulmonary venous anastomotic obstruction, cardiogenic edema, and pneumonia, is recommended; but the exact methodology for exclusion is not specified.[2] In addition to grading severity, the definition also recommends assessing PGD severity daily for the first 72 hours in order to evaluate the natural history of PGD. A few exceptions to the scheme are clarified in the consensus definition. A PGD grade of 0 or 1 (based on chest radiograph) should be assigned to patients using nasal cannula for oxygen or a Fio_2 less than 0.3. The need for extracorporeal oxygenation is considered grade 3. Patients on mechanical ventilation with Fio_2 greater than 0.5 on nitric oxide beyond 48 hours after transplant are categorized as PGD3.

LESSONS LEARNED FROM THE 2005 PRIMARY GRAFT DYSFUNCTION DEFINITION

The 2005 definition highlighted both grade and timing of PGD and encouraged future studies to evaluate the clinical importance of each component of the definition. Compared with PGD grade 0, milder forms of PGD (PGD grades 1 and 2) have been associated with increased mortality and bronchiolitis obliterans syndrome (BOS), a form of chronic allograft dysfunction.[7] However, the impact of PGD on important clinical outcomes, including mortality and chronic lung dysfunction, seems to be consistently strongest for PGD3. PGD3 occurring at any time point after reperfusion is associated with greater alteration in plasma markers of lung injury, higher short- and long-term mortality, and higher rates of BOS than milder forms of PGD.[1,5,7,17] Although some trials use the dichotomous definition of PGD3 alone as the outcome of interest, other trials incorporate milder forms of PGD.

Several trials have attempted to identify the optimal time point at which to grade PGD. PGD3 at 48 and 72 hours demonstrated better mortality discrimination than PGD3 at 24 hours after transplant.[1] Latent class analysis identified 2 main subphenotypes among 361 subjects with PGD3: those with PGD3 that persisted at 72 hours and those with PGD3 that resolved or attenuated to a lower grade by 24 hours.[18] The phenotype with persistent PGD3, likely representing those with true diffuse alveolar damage, was associated with higher cardiopulmonary bypass (CPB) use, more red blood cell (RBC) transfusions, higher mean pulmonary artery pressure (PAP), and higher mortality. Those with PGD3 that attenuated or resolved by 24 hours received a higher volume of intraoperative crystalloids. Using PGD3 at a specific time point as an end point for clinical trials may be useful as it represents a more severe phenotype. However, this must be weighed against the cost of limiting the sample size.

Despite these findings and the good discriminative ability of the 2005 definition, controversy remains in the lung transplant community about the grade and time point of PGD to use for outcomes in clinical and mechanistic trials. This controversy highlights the need for ongoing refinement of the 2005 definition. In 2015, the ISHLT began a second consensus effort to update and refine the PGD definition; therefore, updated criteria should be forthcoming addressing issues including timing of PGD onset and resolution, precision of the P/F at different levels of Fio_2, single versus bilateral transplants, and differences in grading patients with fibrotic lung disease.

Table 1
2005 International Society for Heart and Lung Transplantation primary graft dysfunction definition

Grade	Pao_2/Fio_2	Radiographic Infiltrates Consistent with Pulmonary Edema
0	>300	Absent
1	>300	Present
2	200–300	Present
3	<200	Present

From Christie JD, Carby M, Bag R, et al. Report of the ISHLT working group on primary lung graft dysfunction part II: definition. A consensus statement of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2005;24(10):1454–9.

EPIDEMIOLOGY AND OUTCOMES

The incidence of PGD3 at a single time point has been reported to be between 7.9% and 25.0%, whereas the incidence of PGD3 at any time point during the first 3 days is approximately