Society for Heart Failure and Transplantation

SOCIETY FOR HEART FAILURE AND TRANSPLANTATION'S

THE REVIVAL

Promoting Academics to Improve Clinical Outcomes.

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EDITOR'S NOTE

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Greetings dear Readers of The Revival,

Our guest author Dr Basha Khan has written a brilliant article on Primary Graft Dysfunction after Lung Transplant. The article covers the salient features of PGD post Lung Transplantation including the grading, high risk variables, clinical presentation, evaluation and treatment options. An interesting section of this article worth reading is the differential diagnosis section. The misdiagnosis of PGD with other conditions which could occur concurrently or exclusively are worth noting. These conditions can confound the treatment process if not diagnosed in time. The potential benefits of inhaled prostaglandin (PGE1) in the intra operative and donor preservation fluid will need further evaluation and studies.

I thank Dr Basha Khan for his kind contribution and I wish our dear Readers a Happy Reading as always!

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Dr Talha Meeran

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Dear Colleagues,

This edition of REVIVAL features an excellent article by Dr Basha Khan. Dr Basha has taken on a complex subject pertaining to lung transplant which we all are still learning about.

The review is detailed yet succinct covering all topics related to Primary graft dysfunction post lung transplant. This was an extremely useful read for a cardiologist like myself who does not routinely take care of lung transplant recipients but do frequently see combined heart & lung transplant recipients.

Sincerely,
Dr Talha Meeran
Sub Editor "The Revival"

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Special thanks to Dr Basha J Khan for authoring this month's article.

Designed by Maithili Kulkarni

PRESIDENTIAL MESSAGE

Dr Julius Punnen

Sr. Consultant Cardiothoracic Surgeon, Narayana Health, Bangalore

Dear members of SfHFT,

It is with great pleasure that we delve into a critical aspect of lung transplantation in this edition of our newsletter: primary graft dysfunction (PGD) following lung transplantation. As healthcare professionals committed to advancing the field of thoracic transplantation, it is imperative that we stay abreast of the challenges in organ transplantation to ensure the best possible outcomes for our patients. Lung transplantation stands as a life-saving intervention for patients suffering from end-stage lung diseases. However, the road to recovery for our recipients is not without its hurdles. Among these challenges, primary graft dysfunction emerges as a complex and multifaceted condition which affects a third of patients and has a 30 day mortality exceeding 30% and therefore warrants our utmost attention. The goal with this article is to provide a comprehensive overview of PGD, from its underlying mechanisms to its clinical implications, thereby equipping our members with the knowledge needed to effectively manage and mitigate this complication.

In the pages that follow, Dr Basha Khan in the article will explores the definition, classification and all other aspects of PGD in a very comprehensive and precise manner shedding light on the intricate interplay of immunological, inflammatory, and ischemic factors that contribute to its onset. Moreover, the article will delve into the nuances of diagnosis, risk stratification, and preventive strategies. By synthesizing the most current research and clinical experiences, he aims to empower our readers with evidence-based insights that can guide decision-making and enhance patient care. As we navigate the complexities of primary graft dysfunction, let us remain steadfast in our commitment to advancing the science of thoracic transplantation. By fostering a collaborative exchange of knowledge and ideas, we can drive innovation, refine our practices, and ultimately, improve the lives of those entrusted to our care. Thank you for your unwavering dedication to the Society for Heart Failure and Transplantation. We invite you to explore this article with the same enthusiasm and dedication that defines our shared mission.

With warm regards,

Dr Julius Punnen

President, Society for Heart Failure and Transplantation

PRIMARY GRAFT DYSFUNCTION AFTER LUNG TRANSPLANTATION

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Introduction

Primary Graft Dysfunction (PGD), a severe form of lung injury, commonly manifests within the initial 72 hours following lung transplantation. This complication stands as the leading cause of both early mortality and morbidity post-transplantation. Also referred to as ischemia-reperfusion injury or reperfusion edema, PGD emerges as the most prevalent complication during the initial stages post-transplantation.

With an overall incidence of approximately 30%, the 30-day and 90-day mortality rates for grade 3 PGD stand at 36.4% and 23%, respectively. The risk factors, diagnosis, grading, and strategies to prevent and treat PGD are reviewed here.

DEFINITION AND GRADING

PGD is defined by the presence of diffuse pulmonary opacities on thoracic imaging and hypoxemia without other identifiable causes, developing in the first 72 hours after lung allograft implantation [1]. The primary pathological features of PGD are ischemic pulmonary vascular injury, increased vascular permeability, and diffuse alveolar injury with characteristic hyaline membrane formation and alveolar septal thickening suggestive of diffuse alveolar damage.

The definition of PGD was updated in the 2016 consensus report of the International Society of Heart and Lung Transplantation (ISHLT)'s working group on PGD.

The presence of PGD requires radiographic findings consistent with pulmonary edema and its severity is modeled in part on the definition of the acute respiratory distress syndrome (ARDS). PGD grades are determined by the ratio of the partial pressure of arterial oxygen (PaO2)/fraction of inspired oxygen (FiO2), also called P/F ratio. If the PaO2 is not available, the oxygen saturation (SpO2)/FiO2 or S/F ratio may be utilized instead.

PGD GRADE	PaO2/FiO2	Radiographic infiltrates consistent with pulmonary edema
PGD grade 0 (no PGD):	P/F ratio >300	Absent
PGD grade 1:	P/F ratio >300 or S/F ratio >315	Present
PGD grade 2:	P/F ratio = 200 to 300 or S/F ratio = 235 to 315	Present
PGD grade 3:	P/F ratio <200 or S/F ratio <235	Present

- PGD is assessed at four time points, starting at the time of reperfusion of the second lung (T0), and then at 24, 48, and 72 hours (T24, T48, T72).
- The PaO2/FiO2 is ideally measured on a positive end-expiratory pressure (PEEP) of 5 cm H2O at FiO2 1.0; correction may be needed for high altitude.
- Use of extracorporeal lung support (ECLS) with bilateral pulmonary edema on chest radiograph should be graded as grade 3, and ECLS use should be documented. The use of ECLS for nonhypoxic indications without pulmonary edema on chest radiograph should be considered ungradable.

RISK FACTORS

Multiple stages from preoperative donor acquisition to reperfusion can influence the occurrence of PGD. For example, preoperative donor lung ischemia, organ acquisition, preservation techniques, and intraoperative organ implantation and reperfusion are all risk factors for PGD [2]. In addition, pneumonia and microtrauma associated with mechanical ventilation are also considered as contributing factors.

Category	Risk factors for PGD
Donor Inherent variables	Age>45 yo, Age<21 yo
	African American race
	Female gender
	History of smoking>20py, >10py, current, **any**
Donor acquired variables	Prolonged mechanical ventilation
	Aspiration
	Head trauma
	Hemodynamic instability after brain death
Recipient variables	**Obesity Body mass index>25**
	Female gender
	Diagnosis of idiopathic pulmonary hypertension
	Diagnosis of secondary pulmonary hypertension
	Diagnosis of idiopathic pulmonary fibrosis
	Diagnosis of sarcoidosis
	Elevated pulmonary arterial pressure at time of surgery
Operative variables	**Single lung transplantation**
	Prolonged ischemic time
	Use of cardiopulmonary bypass
	Blood products transfusion>1L
	High FiO2>=0.4 at reperfusion
	Use of Intra-cellular (Hyperkalemic) type (Euro-Collins) preservation solution

Donor risk factors:

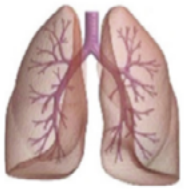
Several factors, such as the donor's smoking history, death due to traumatic brain injury, and advanced age, are associated with an elevated risk of Primary Graft Dysfunction (PGD). Donor Pulmonary Embolism (PE) may potentially serve as a risk factor for PGD; however, studies pertaining to this correlation remain limited. Moreover, a history of heavy alcohol use in donors has been linked to grade 3 PGD.

Recipient risk factors:

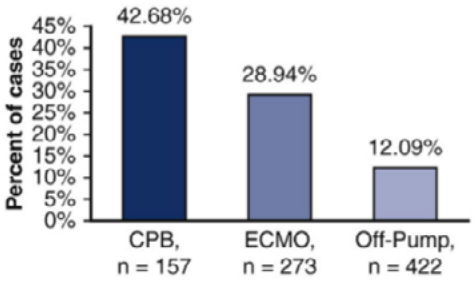
Notable recipient risk factors for Primary Graft Dysfunction (PGD) encompass aspects such as female gender, obesity, diagnoses of primary pulmonary hypertension, sarcoidosis, and idiopathic pulmonary fibrosis (IPF). The risk of PGD escalates with an increase in recipient pulmonary arterial pressure. Genetic variations among recipients, which are connected to the pathogenesis of PGD, have been a point of interest in understanding why certain recipients develop severe PGD while others do not. For instance, specific TLR4 polymorphisms have been linked with a reduced risk of PGD.

The use and type of extracorporeal life support (ECLS) has a significant effect on primary graft dysfunction (PGD): analysis of the international multicenter ECLS in Lung Transplantation Registry

852 bilateral lung transplants across 8 centers



Percent of cases with PGD3 at 48-72 hours after reperfusion by mode of support



Stepwise multiple logistic regression for the effect of mode of support on PGD3 at 48-72 hours

	Odds Ratio	95% Confidence Interval	*P* valve
CPB vs ECMO	1.89	1.05 – 3.41	.033
CPB vs Off-Pump	4.24	2.24 – 8.04	< .001
ECMO vs Off-Pump	2.24	1.38 – 3.65	.001

***CPB*, Cardiopulmonary bypass; *ECLS*, extracorporeal life support; *ECMO*, extracorporeal membrane oxygenation; *Off-pump*, single-lung ventilation and perfusion without ECLS; PGD, primary graft dysfunction**

Other risk factors:

A multitude of perioperative risk factors for Primary Graft Dysfunction (PGD) have been recognized. The intraoperative use of cardiopulmonary bypass dramatically escalates the risk of grade 3 PGD and is generally associated with worse outcomes following lung transplantation [3]. Increased intraoperative red blood cell transfusion has been shown to elevate the risk of persistent grade 3 PGD over the initial 72 hours. Prolonged ischemic time has also been significantly linked with an increased risk of PGD.

CLINICAL MANIFESTATIONS

It's essentially a form of acute lung injury or acute respiratory distress syndrome (ARDS) that specifically occurs in the context of lung transplantation. The clinical manifestations of PGD are similar to those seen in patients with ARDS and can vary in severity.

Hypoxemia: This is one of the most notable clinical manifestations of PGD. It can range from mild to severe and is typically measured by the PaO2/FiO2 ratio (the ratio of arterial oxygen partial pressure to fractional inspired oxygen).

Pulmonary Infiltrates: Another common finding in PGD is the presence of diffuse pulmonary infiltrates on chest imaging, usually seen on chest x-ray or computed tomography (CT) scan. These infiltrates are typically bilateral and may appear as diffuse opacities or "white-out" lungs in severe cases.

Respiratory Distress: Patients with PGD may exhibit signs of respiratory distress, including tachypnea (rapid breathing), dyspnea (shortness of breath), and use of accessory muscles of respiration.

Hemodynamic Instability: In severe cases, PGD can lead to hemodynamic instability, including hypotension and shock.

The clinical course can also vary widely, with some patients recovering quickly while others progress to persistent respiratory failure or death. Severe PGD patients have decreased lung compliance, increased pulmonary vascular resistance, and intrapulmonary shunting. The diagnosis is made after other potential causes of lung dysfunction, such as pneumonia, pulmonary edema, and pulmonary embolism, have been ruled out.

DIAGNOSTIC EVALUATION

In the evaluation of Post-Lung Transplant (LTx) complications, clinicians need to consider factors that could exacerbate or obscure the severity of Primary Graft Dysfunction (PGD). Potential complications include airway issues (stenosis or dehiscence of bronchial anastomoses, impaction), vascular problems (anastomoses obstruction), cardiac conditions (left heart failure, dys-synchrony), parenchymal complications (infection, rejection, aspiration, atelectasis, hemorrhage), and pleural complications (effusion, hemothorax, pneumothorax, open chest).

Radiographic Imaging: Clinical presentations of PGD are often nonspecific and vary widely, most commonly including perihilar and basal airspace consolidations in the middle and lower lobes, interstitial opacities, peribronchovascular and septal thickening, and without evidence of cardiomegaly. Minimal pleural effusion may also be observed.

To better define the pattern of parenchymal opacities, chest computed tomography (CT) is frequently employed. CT or ultrasound may be used to distinguish parenchymal opacities from pleural collections.

Definitive diagnosis generally necessitates the exclusion of other potential confounding causes, such as infection, cardiogenic pulmonary edema, or rejection. In addition to imaging studies, Echocardiogram can help rule out cardiogenic pulmonary edema.

Bronchoscopy: Bronchoscopy is recommended for assessing

airway obstruction due to mucus or blood clots, abnormalities in bronchial anastomosis, and to acquire bronchoalveolar lavage (BAL) fluid samples for microbiologic investigations in patients with PGD. Bronchoscopy also plays a crucial role in identifying rare early surgical complications such as bronchial anastomotic stricture or dehiscence, and whole lung torsion.

These evaluations and interventions serve as essential tools in managing patients with PGD post-LTx, assisting clinicians in identifying the underlying complications and thereby, paving the way for the appropriate therapeutic measures.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of Primary Graft Dysfunction (PGD) encompasses conditions that induce diffuse pulmonary opacities and hypoxemia within the initial 72 hours subsequent to lung transplantation. A patient may simultaneously present with one or more of these processes alongside PGD.

Hyperacute Rejection: This typically manifests in the immediate post-transplant phase, mediated by the binding of preexisting antibodies to graft antigens such as human leukocyte antigen (HLA) or ABO isoagglutinins.

Pulmonary Edema: Hydrostatic pulmonary edema may be induced by left ventricular dysfunction or volume overload.

Pneumonia: Despite prophylactic antibiotic use, Secondary bacterial pneumonia the most common cause of respiratory failure in the immediate post-transplant period.

Occlusion of the Venous Anastomosis: Venous anastomosis thrombosis should be considered if radiography reveals opacity in one of the transplanted lungs.

Pleural Fluid or Hemothorax: Postoperative pleural fluid and hemothorax can induce diffuse opacity on a supine chest radiograph. However, the opacity generally presents more uniformly than with pulmonary parenchymal disease.

Pulmonary Embolism: In Lung Transplant recipients, Pulmonary embolism can have fatal consequences with high risk of pulmonary infarction due to absence of collateral bronchial circulation in immediate post operative period.

TREATMENT OPTIONS

The treatment for Primary Graft Dysfunction (PGD) generally involves supportive measures aimed at maintaining adequate oxygenation and minimizing further lung injury. The treatment options for PGD can vary based on the severity of the condition, and individual patient factors. As PGD likely represents a form of acute respiratory distress syndrome (ARDS) and has many similar clinical, physiologic, radiographic, and pathologic manifestations, supportive care strategies model those utilized for ARDS treatment.

Supportive Care:

Mechanical Ventilation: Patients with severe PGD often require mechanical ventilation to support their respiratory function. This can involve various strategies to optimize oxygenation and reduce potential ventilator-induced lung injury. These include using low tidal volumes, high positive end-expiratory pressure (PEEP), and in certain situations, prone positioning.

Hemodynamic Support: In cases of cardiovascular instability, intravenous fluids, vasopressors, or inotropes may be administered to maintain blood pressure and organ perfusion

Fluid Management: A balance must be struck between maintaining adequate circulatory volume and avoiding fluid overload, which could exacerbate PGD.

PHARMACOLOGICAL INTERVENTIONS

Immunosuppressive Medications: Corticosteroids and other immunosuppressive drugs are often given to reduce the inflammatory response and prevent the body from rejecting the transplanted lung.

Inhaled nitric oxide: iNO has been used as a potential therapy for PGD due to its vasodilatory properties, ability to reduce inflammation and platelet aggregation, and its potential protective effect against ischemia-reperfusion injury. However, the efficacy of iNO in preventing or treating PGD in lung transplant patients is not definitively established. Additionally, ino exposure could theoretically lead to the formation of methaemoglobin (MetHb) and an increased risk of renal failure.

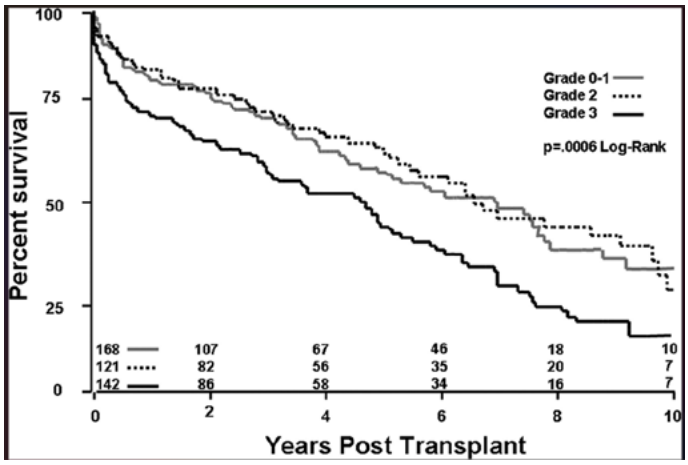
Inhaled prostaglandin: Prostaglandin E1 (PGE1) plays a potential role in managing Postoperative Graft Dysfunction (PGD) due to its vasodilatory effect. It can induce vasodilation by elevating intracellular cyclic adenosine monophosphate (cAMP). In the context of lung transplantation, these vasodilatory effects can be particularly beneficial.The vasodilation effect of PGE1 can improve oxygenation by increasing blood flow in the lungs, thus improving the ventilation-perfusion match. This can help to reduce the severity of PGD, which is a condition characterized by poor oxygenation and lung function following transplantation.

Studies have also examined the use of PGE1 in the intraoperative setting, as well as in the donor lung preservation fluid [4]. These uses of PGE1 aim to improve lung function following transplantation and potentially reduce the incidence or severity of PGD.

However, the exact role of PGE1 in managing PGD is not yet fully understood. While some studies suggest a potential benefit, others have not found the same results.

Extracorporeal Membrane Oxygenation (ECMO): Recent advancements in ECMO (Extracorporeal Membrane Oxygenation) technology and management have significantly improved the outcomes for patients suffering from severe Postoperative Graft Dysfunction (PGD) after lung transplantation. ECMO is recommended for patients with PGD grade 3 who have refractory hypoxemia (eg, partial pressure of arterial

oxygen [PaO2]/fraction of inspired oxygen [FiO2] [P/F ratio] <100 mmHg) despite optimal medical treatment and ventilator settings, ECMO initiation is recommended .In 2023, Takahashi et al. published an article stating that the use of VV ECMO support for PGD grade 3 patients post-lung transplantation resulted in satisfactory short- and long-term outcomes [5]. Their findings suggested that patients who required ECMO support for PGD grade 3 following lung transplantation were significantly more likely to experience perioperative complications in comparison to those with PGD grade 3 who did not necessitate ECMO support. Veno venous (VV) ECMO, the most commonly employed method, incorporates an ECMO circuit consisting of a centrifugal blood pump and an adult microporous membrane oxygenator.



OUTCOME

Several studies have confirmed a correlation between Primary Graft Dysfunction (PGD) and both 90-day and 1-year mortality rates. Specifically, the implications of PGD Grade 3 extend to significantly decreased long-term survival and a higher incidence of Bronchiolitis Obliterans Syndrome (BOS) [6]. The severity of PGD is proportionally related to an increased relative risk of BOS. Beyond survival rates and BOS, research on other long-term outcomes of severe PGD, such as quality of life, is limited.

Conclusion:

Primary graft dysfunction (PGD) is a serious and potentially life-threatening complication that can occur after lung transplantation. PGD remains an area of active research and ongoing efforts are being made to better understand its underlying mechanisms, risk factors, and treatment options. Ultimately, advancements in understanding and managing PGD will contribute to improved patient outcomes and long-term graft survival following lung transplantation.

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