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Primary Graft Dysfunction

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Abstract

Primary graft dysfunction (PGD) is a syndrome encompassing a spectrum of mild to severe lung injury that occurs within the first 72 hours after lung transplantation. PGD is characterized by pulmonary edema with diffuse alveolar damage that manifests clinically as progressive hypoxemia with radiographic pulmonary infiltrates. In recent years, new knowledge has been generated on risks and mechanisms of PGD. Following ischemia and reperfusion, inflammatory and immunological injury-repair responses appear to be key controlling mechanisms. In addition, PGD has significant impact on short- and long-term outcomes; therefore, the choice of donor organ is impacted by this potential adverse consequence. Improved methods of reducing PGD risk and efforts to safely expand the pool are being developed. *Ex-vivo* lung perfusion is a strategy which may improve risk assessment and become a promising platform to implement treatment interventions to prevent PGD. This review will detail recent updates in the epidemiology, pathophysiology, molecular and genetic biomarkers and state-of-the-art technical developments affecting PGD. (158 words)

Keywords

primary graft dysfunction; lung transplantation; ischemia-reperfusion injury and repair; high-risk donor lung; ex-vivo lung perfusion

Definition and Clinical Presentation

Primary graft dysfunction (PGD) is a syndrome of acute lung injury that occurs within the first 72 hours after lung transplantation. PGD is characterized by pulmonary edema with diffuse alveolar damage that clinically manifests itself as progressive hypoxemia and radiographic pulmonary infiltrates without other identifiable causes.[1-8]. PGD is a form of the Acute Respiratory Distress Syndrome (ARDS), and shares characteristics with other factors predisposing to ARDS, such as trauma and sepsis.[9] Historically, various labels were applied to PGD including ischemia-reperfusion injury, re-implantation response and edema, reperfusion edema, non-cardiogenic pulmonary edema, early graft dysfunction, primary

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graft failure, and post-transplant ARDS; however, the taxonomy was standardized in 2005 as PGD.[1,8]

PGD develops progressively and encompasses a spectrum of acute lung injury from milder dysfunction to more severe lung injury. The lack of standard defining criteria for PGD across studies resulted in historical variability in reported incidence rates, risk factors, clinical outcomes, and treatment effects, which led to inconsistencies in reproducibility and generalizability.[1,6-17] Therefore, in 2005, the International Society of Heart and Lung Transplantation (ISHLT) Working Group on PGD proposed a standardized definition and grading system with the intent of establishing a reproducible and robust taxonomy.[1] The proposed standardized definition of PGD was based on radiographic pulmonary infiltrates and a PaO_2/FiO_2 (P/F) ratio assessed at several time points after lung transplantation (Table 1, Figure 1). For example, the presence of radiographic infiltrates consistent with pulmonary edema and a P/F ratio of <200 after 72 hours of final lung perfusion are classified as “T72 Grade 3 PGD.”

The diagnosis of PGD requires exclusion of mechanical, immune and infectious causes that can mimic, modify, and confound definition and grading (Table 2).[1] Ideally, the P/F ratio is measured on a FiO_2 of 1.0 and positive end expiratory pressure (PEEP) of 5 cm H_2O. The ISHLT PGD definition and grading system was intended to be a first step to a continually refined definition (Table 2).[1] Several proposed changes to the standardized definition have been suggested (Table 2)[18-22] and further refinement efforts including validation and pathophysiological correlates are underway.

Radiographic findings of PGD are nonspecific and include perihilar ground-glass opacities, peribronchial and perivascular thickening, and reticular interstitial and airspace opacities located in a dependent fashion predominantly in the middle and lower lung lobes.[23-25] In the majority of cases, parenchymal opacities appear on postoperative day 1 and peak by day 3; however, different patterns of PGD resolution have been described. Clearance of these radiographic abnormalities usually begins on postoperative day 5-10; however, complete clearance is dependent on the severity of injury and can take between 10 days to a few months among survivors.[23-26] Clinical improvement in the A-a gradient and P/F ratio often precedes radiographic resolution and poor correlation of radiographic finding has been reported.[25] Recently, different patterns of PGD resolution have been reported, which may represent different injury resolution phenotypes.[27]

Epidemiology and Outcomes

In the era predating the ISHLT standardized definition, PGD had a reported incidence ranging between 11% and 57% in single-institution studies,[7,9-17] with the more severe PGD (ISHLT grade 3) estimated to be between 15 to 35%.[6] A retrospective analysis of 5262 lung recipients in the United Network for Organ Sharing (UNOS) /ISHLT registry between 1994 and 2000 showed that the overall incidence of T72 Grade 3 PGD was 10.2% without any significant changes by year (8-12% p=0.22); however, these findings were limited by the validity of the definition in this administrative dataset.[28] A recent analysis of 1255 lung recipients enrolled between 2002 and 2010 in a prospective cohort study in 10 U.S. lung transplant centers (the Lung Transplant Outcomes Group: LTOG) showed that the incidence of T48-72 Grade 3 PGD was 16.8% with an overall incidence of Grade 3 PGD at any time point in the first 72 hours of 30.8%.[29] The incidence of T48-72 Grade 3 PGD across the 10 centers varied significantly (2 to 27 %), reflecting different practice patterns and different risk factor distributions across centers. Since the ISHLT standardized definition and grading, the incidence of severe PGD (Grade 3) at T48-72 has been reported about 10-20% and the

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incidence of severe PGD (Grade 3) at any time point in the first 72 hours has been reported about 30% (Table 3).[28-35]

PGD has a significant impact on early morbidity and mortality after lung transplantation, resulting in prolonged length of mechanical ventilation, prolonged intensive care unit (ICU) and hospital stay, increased cost, and increased short-term mortality.[9] The impact of PGD on outcomes after the 2005 standardized definition was implemented is summarized in Table 3.[28-35] Studies using the new definition have demonstrated better discrimination of PGD (Grade 3) to predict mortality in the short-term.[30,31] Grade 3 PGD at T72 compared to Grade 0 demonstrated significantly higher risk of 30 day mortality and accounted for 50% of all-cause mortality within this period.[29,31] When studied at 48-72 hours, Grade 3 PGD has been associated with increased 90 day mortality, with an absolute mortality increase of 18%.[29] This risk persisted to 1 year post-transplant, with an absolute mortality increase of 23% at 1 year.[29] Furthermore, grade 3 PGD is strongly associated with longer-term mortality,[28,30-35] even after conditioning on 1 year survival.[28]

PGD has been associated with bronchiolitis obliterans syndrome (BOS), a significant limiting factor for long-term survival after lung transplantation.[36] Initially, investigations evaluating linkage between PGD and BOS were conflicting before the ISHLT PGD standardized definition.[9,12,13] However, subsequent studies showed this correlation between PGD and BOS to be independently significant, even for intermediate grades of PGD in dose-dependent fashion (Table 3).[32-35] Recently, it was shown that markers of increased epithelial injury during PGD correlate with BOS, perhaps indicating a link between the degree of epithelial injury and aberrant repair or ongoing immune activation leading to BOS.[37] PGD also has a negative impact on functional status. Survivors of T72 Grade 3 PGD at 12 months cover far less distance as measured by 6 minute walk distance than those without Grade 3 PGD.[17] Because Grade 3 PGD has significant impact in short- and long term mortality and function, a thorough understanding of PGD risk may allow significant improvement in outcomes in lung transplant recipients.

Clinical risk factors

Many groups have studied risk factors for development of PGD.[5,10,11,16,20,29,38-58] In the lung transplant process, there are several potentially injurious stages: 1) brain death of the donor, 2) explantation and preservation of donor organ, 3) cold ischemic storage and transport, 4) ischemia reperfusion injury (IRI) of the donor lung with implantation, and 5) postoperative recovery of the recipient.[5] At each of these stages, a clear understanding of the pathophysiology of PGD and the contribution of each risk factor may allow for deliberate strategies and tailored interventions that can be implemented to improve outcomes related to PGD.

Studies examining clinical risk factors for PGD have been commonly limited by small sample sizes, single center designs, reliance on administrative data, and previously inconsistent definitions of PGD.[29] Despite these limitations, several clinical risk factors have been consistently identified across studies, summarized in Table 4. [5,16,29,38-41] These risk factors can generally be categorized as donor, recipient, and operative related (Table 4).[5,16] Donor-related risk factors include inherent (age, gender, race, smoking history) and acquired (primary and secondary injuries resulting from cause of death: pneumonia, aspiration, multiple blood transfusion, volume overload, hemodynamic instability, and ventilation associated injury) conditions which cannot be changed at the time of donor offer but may in the future be mitigated through *ex vivo* conditioning techniques or improved donor-recipient matching strategies.[5,16,29,38-40,43] In particular, the donor smoking history has been a source of controversy, given inherent inaccuracy in determining donor smoking

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status[29] as well as the fact that excluding donors with smoking history from the available pool of donor organs leads to more death for the whole transplant population.[59] Studies of recipient-related factors have consistently reported significant association of diagnosis (idiopathic pulmonary fibrosis, sarcoidosis, and primary pulmonary hypertension), elevated pulmonary arterial pressures, and higher body mass index with PGD.[11,16,29,38,39,41,42,44-46,48-50] These factors are the subjects of ongoing investigations aimed at understanding mechanistic underpinnings of increased PGD risk. Identified operative-related factors include single lung transplant, prolonged ischemic time, intracellular type preservation solutions, blood transfusion and use of cardiopulmonary bypass.[10,20,29,39-41,44,45,47,50-58] Given the complexity of the interaction of multiple risk factors, efforts are currently underway on decision algorithms to aid donor recipient-matching aimed at reducing the incidence of PGD.

Pathogenesis

PGD severity varies depending on (1) the baseline conditions of donor and recipient at the time of selection and matching, (2) conditions imposed on donor and recipient through the events of brain death, explantation, preservation, storage, and implantation, and (3) possibly genetic determinants that may modify injury and repair responses of donor lung in the recipient. The pathogenesis of PGD is complex and consequent to IRI resulting from direct damage of ischemia and preservation, generation of reactive oxygen species (ROS) at reperfusion, and activation of damage-amplifying proinflammatory cascade.

Experimental and clinical evidence suggests that PGD develops in a biphasic pattern with the early phase of PGD depending primarily on cells present in the donor lung and the later phase of PGD resulting from influx of recipient cells.[41] Studies suggest that innate lung macrophages and lymphocytes modulate the early phases of PGD, while influx of recipient neutrophils and lymphocytes become more active in the subsequent later phases.[60-62] Early free radical release from macrophages and pulmonary endothelium promotes the formation of inflammatory agents that recruit and activate recipient neutrophils and lymphocytes, which then escalate the process of injury.[8,60,63-69] Further studies have implicated downstream effectors such as tumor necrosis factor (TNF)-alpha, interleukin (IL)-17 and other mediators of leukocyte, neutrophil, and innate immune components to be important in the recipient response of PGD. [61,70,71]

Human studies using bronchoalveolar lavage or tissue biopsy samples have shown increased levels of IL-8 in the lungs of brain-dead donors that correlate in a dose-dependent manner with PGD severity and mortality.[72] Immunolocalization measurements demonstrate diffuse IL-8 expression within donor lung tissue, with alveolar macrophages and epithelial cells being important sources. This abundant resident population of macrophages that act as a defense mechanism against environmental pathogens may act as a central mediator of the donor and recipient interplay leading to PGD in lung transplantation.

Lung transplantation is unique in that lungs continue to consume oxygen in the alveoli and to maintain aerobic metabolism during the ischemic preservation and storage period.[73,74] This process is associated with higher oxygenation function and higher alveolar fluid clearance after reperfusion independent of the presence of aerobic metabolism.[75,76] In theory, this partial alveolar oxygenation in the donor lung seems to be beneficial; however, multiple studies have demonstrated that it can have detrimental effects.[73,77-80] High oxygen tension in the hypothermic lung is associated with excess ROS generation and lung injury, therefore, the practice of inflated lung procurement with room air is supported by the finding that hypothermic, hyperoxic, atelectatic lungs have worse gas exchange, edema, and peak inspiratory pressure.[75,7680,81] ROS generation is likely the direct result of tissue injury via

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oxidative damage to lipids, proteins, deoxyribonucleic acids, and biomolecules enhanced by the release of free iron Fe^{2+}.[82] Indirect effects have been demonstrated where ROS can serve as a cell signaling mediator responding to the loss of pulsatility by amplifying downstream events which result in endothelial activation.[77-79]

The long-term effects of PGD, particularly with respect to BOS, are also not fully understood. There is some recent evidence that recipients with pretransplant antibodies to self-antigens (k-alpha-1 tubulin, collagen type V, and collagen I) have increased risk of PGD , elevated proinflammatory mediators during the early post-transplant period, increased development of de novo anti-human leukocyte antigen (HLA) type II alloantibodies, and BOS.[83-86] Likewise, there is speculation that PGD induces proinflammatory cascade to up-regulate HLA-II antigens and promoting donor specific alloimmunity, therefore mechanistically linking PGD and BOS,[84-86] but this requires further study.

Molecular and genetic biomarkers

Investigations of clinical biomarkers, mediators, and genetic variants have largely been drawn from prior knowledge of basic pathophysiological mechanisms gained from basic cell and animal studies,[5] and have included markers of alveolar epithelial and endothelial injury, cytokines and chemokines, adhesion molecules, indicators of hypercoagulability and impaired fibrinolysis, markers of vascular permeability and cell proliferation, markers of intracellular assembly for homeostasis and signaling, and markers of innate and acquired immunity. A number of biomarkers and genetic variants have been studied in clinical PGD (Tables 5 and 6),[44,49,71,72,87-113] providing support that these mechanisms are contributing to clinical PGD, and that some may be amenable to targeted therapy. For example, it was recently shown that plasma long pentraxin 3 (PTX3), a readout of innate immune activation is elevated in PGD, and that functional variants in the encoding gene (*PTX3*) predispose to PGD.[103,113] These results may define a population for intervention targeting this mechanistic axis. However, despite these studies, efforts at using markers to clinically predict the development, diagnosis, or prognosis of PGD are incomplete to date.[107]

Preventive Interventions

Strategies commonly used to prevent and minimize the development and severity of PGD include: 1) optimizing selection, matching, and management of donors and recipients preoperatively; 2) improving lung preservation and storage techniques; and 3) improving lung implantation and reperfusion techniques based on known risk factors of PGD.[8,40,41,114,115]

Several therapeutic agents have been investigated in an effort to reduce the incidence of PGD, including:[5] 1) agents replacing endogenous cytoprotective substances including prostaglandins, nitric oxide (NO), surfactant, endothelium-derived relaxing factor, and adenosine; 2) agents inhibiting proinflammatory mediators including Platelet Activating Factor 1 inhibitor and inhibitors of ROS; 3) agents inhibiting neutrophil and neutrophil derived mediators including inhibitors of ROS, cytokines (TNF-alpha, IL-1b), proteases, lipid mediators, adhesion molecules, and complement cascade.[5,8,114,116] However, there have been only a few randomized trials, usually with limited sample sizes.[5] These small trials have failed to definitively demonstrate efficacy and remain an area of intense study,[98,117-122] even though some studies have shown modest improvements in early clinical outcomes with use of inhaled NO (iNO),[98] surfactant,[122] soluble complement receptor 1 inhibitor,[119] and platelet activating factor antagonist.[120]

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Treatment options after diagnosis of PGD

Therapy for established PGD after diagnosis remains generally supportive, and is influenced by those applied in patients with ARDS, including lung-protective ventilation strategies, avoidance of excess fluid administration, iNO or prostacycline, and extracorporeal membrane oxygenation support (ECMO).[114] Although retransplantation can be considered in highly selected cases without other end-organ damage, predicted survival is poor;[123] therefore, retransplantation for PGD is generally not recommended.[114] Protocolized respiratory and hemodynamic management guidelines are feasible and may be effective in reducing the severity of PGD.[124] However, there have been few studies systematically evaluating the application of strategies that have been specifically used in ARDS patients to patients with severe PGD and thus management is largely individualized by center.[29]

There are several animal studies and case series that have demonstrated improved outcomes with iNO administration to prevent and treat severe PGD and refractory hypoxemia in lung transplantation.[125-128] However, there are also conflicting results in randomized controlled studies showing lack of efficacy for iNO use in the clinical setting.[117,118] While use of iNO to prevent PGD has not been established, a randomized clinical trial showed lower incidence of Grade 3 PGD within 72 hours (17.2% vs 45% $p<0.035$) and decreased levels of inflammatory biomarkers with use of iNO beginning at time of transplantation through 48 hours postoperatively.[98] Though iNO does not have an established role in either prevention of PGD development or treatment of established PGD, its use may be justified as salvage therapy in selected cases.

Veno-arterial (VA) ECMO has been used for salvage of refractory hypoxemia due to severe PGD following lung transplantation.[129-132] Veno-venous (VV) ECMO has gained in popularity with potentially good survival if started early.[133] In the past, patients receiving VV ECMO or VA ECMO had poor long-term survival with 30 day, 1 year, and 5 year survival of 55-58%, 39-42%, and 22-29%, respectively.[132] However, the more recent development of high performance membranes and coated circuits has led to improved results. Early VV ECMO achieved significantly improved 30 day, 1 year, and 5 year survival of 82%, 64%, and 49%, respectively.[133] Though survival has improved, allograft function is considerably worse than in transplant recipients not requiring ECMO (peak forced expiratory volume in 1 second: 58% in ECMO vs 83% in non-ECMO, $p = 0.001$), although these results are hampered by intrinsic differences in lung injury between comparator groups.

Extended criteria donor lungs

Procurement rates of lungs offered for transplantation remain between 14-17% of organ donors. Only 31% of patients on the waiting list receive lung transplantation, while 7% die on the list and an additional 8% are removed from the list due to clinical deterioration.[134] Efforts to expand the donor pool by using extended criteria donor lungs have continued since the report of successful marginal donor use by Kron et al in 1993.[135] The reported proportion of extended criteria donor lungs in single institution studies varies between 24-77%, although it is difficult to consistently define an extended criteria donor.[115] Most reports demonstrate equivalent outcomes regarding incidence of PGD, early hospital morbidity and survival, and intermediate survival and freedom from BOS using extended criteria donors.[115,135-144] However, two studies reported a significantly higher incidence of Grade 3 PGD and a significantly higher early organ-specific mortality with the use of extended criteria donor lungs.[140,143] Caution and clinical judgment are needed when using marginal donor lungs with more than one extended criterion and when matching marginal donor lungs to high-risk recipients, especially recipients with pulmonary hypertension.[145]

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Donor-recipient matching is complex in clinical practice and difficult to study because risk assessment is required on an individual case basis. It is unclear how far a given donor can safely be from “ideal criteria” because many factors (donor, recipient and operative) affect the risk and severity of PGD.

Emerging concepts

Normothermic *ex vivo* lung perfusion (EVLP) is a new evaluation technique for high-risk donor organs.[146] EVLP is thought to reduce the risk of using high-risk donor lungs by allowing for an extended normothermic evaluation period. The EVLP system consists of a ventilator and an *ex vivo* circulation system with centrifugal pump, oxygenator, heat-exchanger, and leukocyte filter.[147] Steen and colleagues in Lund, Sweden were the first to successfully apply *ex vivo* evaluation in 2001 on lungs from a donation after cardiac determination of death (DCDD).[148] Following this success, additional study and modification has occurred. In a landmark trial from Toronto, Cypel and colleagues reported excellent clinical outcomes using high-risk donors ordinarily not transplantable with acellular perfusate and protective perfusion and ventilation strategies in 2011.[146] Worldwide clinical experiences with EVLP are summarized in Table 7.[146,149-154] Although most reports are small case series, the proportion of high-risk donor lungs transplanted after EVLP evaluation range between 46-87% resulting in equivalent short-term outcomes as compared with standard criteria donors. It is remarkable that the incidence of severe PGD is generally lower in the EVLP group in comparison to the conventional group, with equivalent survival (96%, 87%, 70% at 30 days, 1 year, and 3 years, respectively). These results demonstrate that EVLP not only enhances the ability to accept more organs for transplantation but also suggests the possibility of reducing the risk of PGD. EVLP might also offer a platform to use targeted therapeutics to enhance the quality of these organs in the future.[155] Further clinical assessment of the impact on PGD and short-term outcomes is underway in a multicenter prospective trial in the United States.

Alternatively, other approaches have been developed that challenge standard organ preservation methods. Warnecke et al, have reported results using a mobile normothermic ex vivo perfusion system designed to minimize cold ischemic injury.[156] Among the 12 donors enrolled, five (42%) were designated extended criteria donors. Median mechanical ventilation time and ICU length of stay post-transplant was 21 hours (range 9.5-456) and 7 days (2-31 days), respectively. All were discharged and one died on day 140 due to cardiomyopathy. Based on these results, a prospective randomized multicenter trial is now underway to compare this method with standard static cold storage.[156]

Conclusions

PGD remains a key factor for both short- and long-term outcomes and thus limits the number of high-risk donor lungs utilized. Implementation of the ISHLT standard definition and grading criteria of PGD has enhanced our ability to better study and understand the incidence, related outcomes, risk factors, biomarkers and genetic factors influencing of PGD. Following ischemia-reperfusion, inflammatory and immunologic injury-repair responses appear to be key controlling mechanisms in PGD. Continued need to safely increase the donor lung pool has driven the development of EVLP as a deliberate strategy to assure the quality of donor lungs and potentially to implement treatment interventions. Initial clinical experience with EVLP looks promising. The impact on long-term outcomes warrants further study and the impact on incidence of PGD will need to be assessed in multicenter prospective trials.

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Abbreviations

ARDS	acute respiratory distress syndrome
BOS	bronchiolitis obliterans syndrome
DCDD	donation after cardiac determination of death
ECMO	extracorporeal membrane oxygenation support
EVLP	ex vivo lung perfusion
HLA	human leukocyte antigen
ICU	intensive care unit
IL	interleukin
IRI	ischemia reperfusion injury
ISHLT	International Society of Heart and Lung Transplantation
LTOG	Lung Transplant Outcomes Group
NO	nitric oxide
PEEP	positive end expiratory pressure
P/F ratio	PaO_2 (the partial pressure of oxygen in alveolar gas)/FiO_2 (the fraction of inspired oxygen) ratio
PGD	primary graft dysfunction
PTX3	long pentraxin 3
ROS	reactive oxygen species
TNF	tumor necrosis factor
UNOS	United Network for Organ Sharing
VA	veno-arterial
VV	veno-venous

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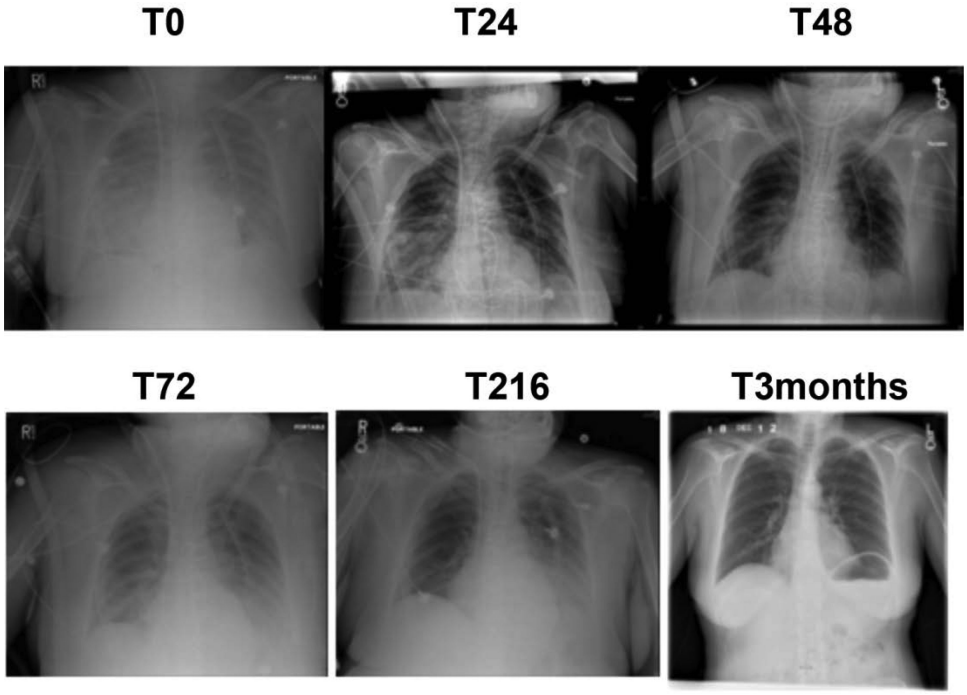

Fig. 1.

Radiographic progression of severe grade 3 primary graft dysfunction (at T0, T24, T48, T72, T216 after extubation, and T3 months) after bilateral sequential lung transplantation with unexpected massive fat embolism of the lungs of a 22-year-old donor from motor vehicle accident. The recipient was a 62-year-old female with emphysema who required 4 days of venovenous extracorporeal membrane oxygenation, 8 days of ventilator support, and 22 days of hospital stay. She recovered with a good functional activity.

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Table 1

2005 ISHLT Primary Graft Dysfunction Taxonomy

Grade at T0, T24, T48, T72	Radiographic infiltrates consistent with diffuse pulmonary edema	PaO_2/FiO_2	Specific exceptions
0	-	Any	
1	+	>300	On nasal canula or FiO_2<0.3
2	+	200-300	
3	+	<200	Any patients on ECMO or on NO with FiO_2>0.5 MV

Adapted from Reference[1]

T0 is defined as within 6 hours of final lung reperfusion or at the admission to the ICU. Patients are not considered having primary graft dysfunction without radiographic infiltrates.

PaO_2/FiO_2 should ideally be measured on PEEP of 5 cm H_2O at FiO_2 of 1.0 while patients are on MV.

ECMO: extracorporeal membrane oxygenation support, FiO_2: fraction of inspired oxygen, ICU: intensive care unit, ISHLT: International Society of Heart Lung Transplantation, NO: nitric oxide, MV: mechanical ventilator, PaO_2: partial arterial oxygen tension (mmHg), PEEP: positive end expiratory pressure

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Table 2

Exclusion Criteria, Limitations, and Refinements of 2005 ISHLT PGD Taxonomy

Exclusion criteria
Cardiogenic pulmonary edema
Pneumonia and aspiration
Hyperacute rejection
Pulmonary venous anastomotic obstruction
Limitations
Exclusion pathology can be missed clinically
Exclusion pathology can exist at the same time
Interobserver reliability of CXR reading
Variability in clinical settings
example: single vs bilateral lung transplantation
patients intubated vs extubated
extubated on just oxygen mask vs on CPAP support
arterial line removed, no P/F ratio measurements available
Variability in clinical conditions
example: mode of ventilation and ventilator settings
changes in cardiac output
Variability in logistics
example: multiple blood gas results close to the time point
Proposed Refinements
T6 and T12 can be added (utility not yet validated)
Early trends in P/F ratio (the percentage change in P/F from T0 to T12) can be added (the utility not yet validated)
Type of the lung transplantation procedure separately designated (single vs bilateral)
Only include bilateral and diffuse infiltrates on CXR in bilateral lung transplantation
Extubated patients with non-invasive ventilation support included
Mode and conditions of ventilation appended
Use P/F ratio not worst, but closest to the time points among available multiple measurements

Adapted from References[1,18-22]

CPAP: continuous positive airway pressure, CXR: chest X-ray, ISHLT: International Society of Heart Lung Transplantation, P/F: PaO_2: arterial oxygen tension (mmHg)/FiO_2: fraction of inspired oxygen, PGD: primary graft dysfunction

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Table 3

The Impact of PGD on Outcomes Using the 2005 ISHLT PGD Taxonomy

First Author	**Prekker[30]**	**Christie[28]**	**Christie[31]***	**Kreisel[32]**	**Diamond[29]**	**Daud[33]**	**Huang[34]**	**Whitson[35]**
Center	Minneapolis	UNOS/ISHLT Registry	Philadelphia	St.Louis	LTOG Registry	St. Louis	St. Louis	Minneapolis
Published	2006	2005	2010	2011	2013	2006	2008	2007
Study dates	1992-2004	1994-2000	1991-2005	1988-2009	2002-2010	1998-2004	1998-2004	1992-2005
Number of subjects	402	5262 (UNOS/ISHLT registry)	446	1000 186 (19%) single vs 805 (81%) bilateral	1255	334	334 26 (7.8%) single vs 308 (92.2%) bilateral	374 (90 day survivors) out of 448 242 (65%) single vs 132 (35%) bilateral
Definition	T0-48 Grade1-3	T72 Grade3 equivalent	T24-72 Grade1-3	T0-48 Grade>3 (P/F<150)	T48-72 Grade3	T0 Grade0-3	T24-72 Grade 0-3	T0-48 Grade0-3
Incidence	25% (T0G3) 15% (T48G3)	10.2% (T72G3)	28% (T24G3) 23% (T48G3) 18% (T72G3)	22.1% (T0-48G>3)	16.8% (T48-72G3) 30.8% (T0-72G3)	19% (T0G0) 39% (T0G1) 21% (T0G2) 21% (T0G3)	15.9% (T24G2) 7.9% (T48G2) 6.4% (T72G2) 16.2% (T24G3) 9.4% (T48G3) 7.9% (T72G3)	32% (T0-48G3)
Mortality (short-term)	90 day mortality 7% (T48G1) 13% (T48G2) 33% (T48G3) (p=0.0001)	30 day mortality 42.1% (T72G3) (RR=6.95 p<0.001) 43.6% attributable to 30 day mortality	30 day mortality 4.2% (T24G0) 3.5% (T24G1) 6.2% (T24G2) 24.5% (T24G3) 3.5% (T72G0) 5.0% (T72G1) 6.1% (T72G2) 36.4% (T72G3) (p<0.001)	Hospital mortality 6.1% (overall) 14% (PGD) 4.0% (nonPGD) (p<0.001) 1 year survival 85% (overall) 73% (PGD) 87% (nonPGD) (p<0.001)	90 day mortality 23% (T48-72G3) RR=4.8 ARI=18% (p<0.001) 1 year mortality 34% (T48-72G3) 11% (the other) RR=3.0 ARI=23% (p<0.001)	90 day mortality 4.2% (overall) 0% (T0G0) 4% (T0G1) 1% (T0G1) 11%(T0G3) (p=0.004)	NS	NS
Mortality (long-term)	G3 worse	T72G3 worse even conditional on survival at 1 year	G3 worse T72G3 more pronounced differences than T24G3	Survival 58% at 5yrs, 33% at 10 yrs (overall) 44% at 5yrs, 19% at 10 yrs (PGD) 60% at 5yrs, 36% at 10 yrs (nonPGD)	NS	T0G3 worse even conditional on 90 day survival	T24-72G3 and T48-72G2 worse even conditional on 90 day survival in univariate analysis RR=2.43 p=0.03 (T48G2) RR=3.27 p=0.003 (T72G2) RR=2.57 p=0.007 (T24G3) RR=4.09 p<0.0005 (T72G3)	G3 worse in bilateral (no difference in single) Survival 66% at 5yrs 38% at 10 yrs (G1) 64% at 5yrs 35% at 10 yrs (G2) 51% at 5yrs 11% at 10 yrs (G3)

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First Author	Prekker[30]	Christie[28]	Christie[31]*	Kreisel[32]	Diamond[29]	Daud[33]	Huang[34]	Whitson[35]
	T0G3 best predicted long-term mortality	(HR=1.35 p=0.011)	T72G1-2 worse than T72G0	(p<0.001)		RR=1.92 p=0.04 (T0G3)	compared to G0 at each T	(p=0.001)
BOS and Function (long-term)	NS	NS	NS	Median time to BOS 3.4 yrs Freedom from BOS 84% at 1yr, 38% at 5yrs, 12% at 10 yrs (overall) 78% at 1yr, 28% at 5yrs, 8.5% at 10 yrs (PGD) 85% at 1yr, 41% at 5yrs, 13% at 10 yrs (nonPGD) (p<0.01)	NS	BOS stage1 incidence 50.3% (161/320) even conditional on 90 day survival Median time to BOS 3.89 yrs PGD was independent risk factor of BOS stage1 RR=1.73 p=0.03 (T0G1) RR=2.13 p=0.004 (T0G2) RR=2.53 p=0.001 (T0G3) compared to T0G0	T24-72G1-3 BOS stage1 RR=1.93 p=0.016 (T24G1) RR=2.29 p=0.008 (T24G2) RR=3.31 p<0.0005 (T24G3) RR=2.07 p=0.003 (T72G1) RR=2.81 p=0.003 (T72G2) RR=4.25 p<0.0005 (T72G3) BOS stage 2 RR=7.24 p<0.0005 (T72G3) BOS stage 3 RR=7.99 p=0.0005 (T72G3) compared to G0 at each T	G3 worse in BOS-free survival rate and mean FEV1 in bilateral (no difference in single)

Adapted from References[28-35]

ARI: absolute risk increase, BOS: bronchiolitis obliterans syndrome, FEV1: forced expiratory volume in 1 second, G: grade, HR: hazard ratio, ICAM-1: intercellular adhesion molecule 1, ISHLT: International Society of Heart Lung Transplantation, LTOG: Lung Transplant Outcomes Group, NS: not stated, PAI-1: plasminogen activator inhibitor 1, P/F: PaO_2: arterial oxygen tension (mmHg)/FiO_2: fraction of inspired oxygen, PGD: primary graft dysfunction, RR: risk ratio, T: time point (hours), UNOS: United Network of Organ Sharing

*Severity grade of PGD was correlated to the level of established biomarkers (Protein C, PAI-1, and ICAM-1).

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Table 4

Clinical Risk Factors for PGD

Category	Risk factors for PGD
Donor inherent variables	Age>45yo, Age<21yo 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 FiO_2 >=0.4 at reperfusion** Use of intra-cellular (hyperkalemic) type (Euro-Collins) preservation solution

Adapted from References[5,16,29,39-41]

Bold: independent risk factors for PGD in LTOG Multicentered Study[29]

FiO_2: fraction of inspired oxygen, LTOG: Lung Transplant Outcomes Group, PGD: primary graft dysfunction, py: pack year, UNOS: United Network of Organ Sharing, yo: year old

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Table 5

Biomarkers for PGD in Human Lung Transplantation

First author, Publication year	Biomarker	Function
Pharm,[87] 1992	IL6	Proinflammatory cytokine
Mal,[71] 1998 Mathur,[88] 2006	IL6, IL8, IL1b, TNFa	Proinflammatory cytokine
Fisher,[72] 2001 De Perrot,[89] 2002	IL8	Chemokine involved in neutrophil recruitment
Colombat,[90] 2004 Kawut,[44] 2009	P-Selectin positive platelet aggregate sP-Selectin	Platelet adhesion molecule on the surface of activated endothelium
Abraham,[91] 2002 Krenn,[92] 2007	VEGF-A and –B VAGF	Regulator of vascular permeability and angiogenesis
Christie,[93] 2007	Protein C PAI1	Anticoagulant Inhibitor of fibrinolysis
Covarrubias,[94] 2007	ICAM1	Adhesion molecule expressed by type I alveolar epithelial cell, alveolar endothelium, and neutrophil
Bobadilla,[95] 2008 Iwata,[96] 2008	Collagen type V IgG Antibody to Collagen type V	Cryptic self-antigen and inducer for specific IL17 dependent cellular autoimmunity
Hoffman,[97] 2009	MCP1(CCL2) IP10/CXCL10 IL13 IL2R	Chemokines involved in monocyte and lymphocyte recruitment Anti-inflammatory and pleiotropic cytokine Proinflammatory cytokines that activates lymphocyte
Moreno,[98] 2009	IL6, IL8 IL10	Proinflammatory cytokine Antiinflammatory cytokine
Christie,[99] 2009 Pelaez,[100] 2010	sRAGE	Marker of type I alveolar epithelial cell injury
Salama,[101] 2010	Endothelin1	Vasoconstrictive peptide, Regulator of vascular permeability
Lederer,[49] 2011	Leptin	Proinflammatory cytokine produced by adipose tissue regulating adipose tissue mass and contributing to acute lung injury and fibroprolifration leading to lung fibrosis
Diamond,[102] 2011	CC16	Marker of lung epithelial injury produced by non-ciliated lung epithelium clara cell
Diamond,[103] 2011	PTX3 in IPF	Phylogenetically conserved acute phase reactant involved in inflammation and innate immunity
Diamond,[104] 2012	Angiopoietin2 in IPF	Inducer for increased endothelial permeability
Bastarache,[105] 2012	Estradiol in male	Proinflammatory female sex hormone
Shah,[106] 2012	MCP1(CCL2)	Chemokines recruiting monocyte, memory T cell, and natural killer cell
Shah,[107] 2012	sRAGE PAI1 ICAM1	Marker of epithelial injury Inhibitor of fibrinolysis Adhesion molecule

Adapted from References[44,49,71,72,87-107]

a: alpha, b: beta, CC16: serum clara cell protein 16, CCL2: chemokine (C-C motif) ligand 2, CXCL10: chemokine (C-X-C motif) ligand 10, ICAM1: intercellular adhesion molecule 1, Ig: immunoglobulin, IL: interleukin, IP10: interferon-gamma induced protein 10, IPF: idiopathic pulmonary fibrosis, MCP1: monocyte chemotactic protein 1, PAI1: plasminogen activator inhibitor 1, PGD: primary graft dysfunction, PTX3: pentraxin 3, RAGE: receptor for advanced glycation end-products, s: soluble, TNF: tumor necrotic factor, VEGF: vascular endothelial growth factor

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Table 6

RNA and DNA Markers for PGD in Human Lung Transplantation

First author, Publication year	Marker	Function
Fisher,[72] 2001	IL-8	Chemokine involved in neutrophil recruitment
Taghavi,[108] 2002	Endothelin-1	Vasoconstrictive peptide, Regulator of vascular permeability
Kaneda,[109] 2006	IL6:IL10 ratio	Proinflammatory: Anti-inflammatory and pleiotropic cytokine
Ray,[110] 2007	Metallothionein 3 (protective)	Intra-cellular protein with antioxidant properties promoting cell proliferation and re-epithelialization
Anraku,[111] 2008	ATP11B FGFR2 EGLN1 MCPH1	ATP-dependent ion transporter for oxidative stress Receptor for HGF and KGF for alveolar epithelial repair Hypoxia-inducible factor (sensor) for controlling hypoxia DNA damage modulation for repairing damaged DNA
Hagedorn,[112] 2011	Autoantibody (IgM) to 17 proteins and donor lung gene expression	12 proteins out of 17 related to cell proliferation
Diamond,[113] 2012	PTX3	Phylogenetically conserved acute phase reactant involved in inflammation and innate immunity

Adapted from References[72,108-113]

ATP: adenosine triphosphate, DNA: deoxyribonucleic acid, HGF: hepatocyte growth factor, IL: interleukin, KGF: keratinocyte growth factor, Ig: immunoglobulin, PGD: primary graft dysfunction, PTX3: pentraxin 3, RNA: ribonucleic acid, SNP: single nucleotide polymorphism

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Table 7

Clinical Experiences of EVLP

Recipients of EVLP reconditioned donor lungs vs Recipients of conventional donor lungs

First Author	Lindstedt[149]	Cypel[146]	Cypel[150]	Zych[151]	Aigner[152]	Valenza[153]	Wallinder[154]
Place	Lund, Sweden	Toronto, Canada	Toronto, Canada	Harefield, England	Vienna, Austria	Milano, Italy	Gothenburg, Sweden
Publication Year	2011	2011	2012	2012	2012	2012	2012
Study Year (duration)	2006-2007	2008-2010 (17 months)	2008-2011 (39 months)	2009-2010 (24mo)	2010-2011 (16 mo)	2011 (6 mo)	2011 (10 mo)
Number of recipients transplanted	6 after 9 EVLP (67%) vs 15	20 after 23 EVLP (87%) vs 116	50 after 58 EVLP (86%) vs 253	6 after 13 EVLP (46%) vs 86	9 after 13 EVLP (69%) vs 119	2 after 2 EVLP (100%) vs 4	6 after 6 EVLP (2/6 double to single) vs 27
Duration of EVLP	1.5-2.0 (hrs)	4.0 (hrs)	4.0-6.0 (hrs)	2.4+-0.5 (hrs)	2-4 (hrs)	4.0 (hrs)	2.6-6.6 (hrs)
Proportion of DLTXP	100% vs 100%	70% vs 85%	76% vs 88%	100% vs NS	100% vs NS	100% vs 100%	67% (4/6) vs NS
Proportion of DCDD	0% vs 0%	45% (9/20) vs NS	44% (22/50) vs 5.1% (P=0.0001)	33% (2/6) vs 23% (3/13)	0% vs NS	0% vs 0%	0% vs NS
Time from Harvest to Implantation (min)	NS	653 (267-1021) vs 370 (163-662)	NS	493 (249-620) vs NS	577 (486-678) vs NS	1005+-21 vs 606+-88	864 (782-1049) vs NS
PaO_2:FiO_2 ratio	NS	335 before EVLP, Among DCDD 275 (160-459) before EVLP	334 (143-532) before EVLP vs 452 (256-590) before conventional (P=0.0001)	317.7+-106.7 before 429.9+-68.3 after EVLP vs NS	216 (133-271) before 466 (434-525) after EVLP vs 447 (311-702) before conventional	184+-6 before EVLP vs 570+-30 before conventional	175.5 (77.4-313.5) before EVLP vs NS
PaO_2:FiO_2 in ICU	NS	422 (85-538) at T0, 414 at T24, 443 at T72	372 (49-591) at T0	291+-56.3 vs NS		218+-32 vs 310+-97 at T0, 306 (282-331) vs 323 (270-396) at T72	
T72 PGD2 or 3	NS	15% vs 30% (P=0.11)	2% vs 8.5% (P=0.14)	NS	0% vs NS	0% (0/2) vs 25% (1/4)	17% (1/6) vs NS
T72 PGD3	NS	0% vs 9.4% (P=0.36)	NS	NS	11% (1/9) vs NS	0% vs 0%	0% vs NS
ECMO	17% (1/6) vs 27% (4/15)	0% vs 4%	2% vs 2.7%	33% (2/6) vs NS	11% (1/9) vs NS	0% vs 0%	0% vs NS
Ventilation time (day)	NS	2 (1-101) vs 2 (1-43)	2 (1-101) vs 2.2 (1-43)	11+-12 vs NS	2 (1-7) vs 1 (1-47)	NS	1 (1-24) days vs NS
ICU stay (day)	13(IQ 5, 24) vs 7 (IQ 5, 12) (P=0.44)	4 (1-101) vs 4 (1-103)	4 (1-100) vs 4.5 (1-257)	20.5 (IQ 4.0, 50.5) vs 7 (IQ 3.0, 25.5)	5.5 (3-18) vs 6 (2-51)	6 (3-9) vs 27 (5-50)	3.5 (2-27)
Hospital stay (day) median	52 (IQ 47, 60) vs 44 (IQ 37, 48) (P=0.9)	23 (7-101) vs 27 (9-156)	20 (7-156) vs 23 (1-299)	38 (IQ 25, 67.5) vs 37 (IQ 24, 59.5)	20 (14-59) vs 20.5 (12-90)	34+-20 vs 46+-33	26 (25-44) vs NS

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First Author	Lindstedt[149]	Cypel[146]	Cypel[150]	Zych[151]	Aigner[152]	Valenza[153]	Wallinder[154]
Survival	100% at 30 days 100% at 3 months 83% at 6 months 67% at 1 year	90% (18/20) vs 94.8%(110/116) at 30 days (P=0.33) 80% vs 83.6% at 1 year 75% at 561 days (7-821) vs 81% at 542 days (9-828)	96% (48/50) vs 96.5% (244/253) at 30 days 87% vs 86% at 1 year 70% vs 72% at 3 year	100% vs 90% at 3 months 83% vs 88% at 6 months	100% vs 95.8% at 30 days 89% vs NS at 3 months 89% vs NS at 6 months 78% vs NS at 1 year	100% (2/2) vs 100% (4/4) at 30 days 50% (1/2) vs 75% (3/4) at 3 months	100% (6/6) vs NS at 30 days

Adapted from References[146,149-154]

<median (range minimum-maximum) or median+-standard deviation, IQ:interquartile range (IQ25, IQ75)>

DCDD: donation after cardiac determination of death, DLTXP: double lung transplantation, ECMO: extracorporeal membrane oxygenation support, EVLP: ex-vivo lung perfusion, hrs: hours, ICU: intensive care unit, min: minutes, mo: months, PGD: primary graft dysfunction, PaO_2: arterial oxygen tension (mmHg), FiO_2: fraction of inspired oxygen, T72PGD3: PGD grade 3 at 72 hours after lung transplantation