Review Article on Lung Transplantation: Past, Present, and Future

Primary graft dysfunction: what we know

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Abstract: Many advances in lung transplant have occurred over the last few decades in the understanding of primary graft dysfunction (PGD) though effective prevention and treatment remain elusive. This review will cover prior understanding of PGD, recent findings, and directions for future research. A consensus statement updating the definition of PGD in 2016 highlights the growing complexity of lung transplant perioperative care taking into account the increasing use of high flow oxygen delivery and pulmonary vasodilators in the current era. PGD, particularly more severe grades, is associated with worse short- and long-term outcomes after transplant such as chronic lung allograft dysfunction. Growing experience have helped identify recipient, donor, and intraoperative risk factors for PGD. Understanding the pathophysiology of PGD has advanced with increasing knowledge of the role of innate immune response, humoral cell immunity, and epithelial cell injury. Supportive care post-transplant with technological advances in extracorporeal membranous oxygenation (ECMO) remain the mainstay of treatment for severe PGD. Future directions include the evolving utility of *ex vivo* lung perfusion (EVLP) both in PGD research and potential pre-transplant treatment applications. PGD remains an important outcome in lung transplant and the future holds a lot of potential for improvement in understanding its pathophysiology as well as development of preventative therapies and treatment.

Keywords: Primary graft dysfunction (PGD); lung transplant; risk factors

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Introduction

Interest in primary graft dysfunction (PGD) persists in the lung transplant community as progress has highlighted both its complexity and long-term impact on post-transplant outcomes. PGD is a syndrome of acute lung injury in the first 72 hours following lung transplant that is scored based upon graft performance similar to PaO_2:fraction inspired oxygen (P:F) ratio in acute respiratory distress syndrome (ARDS). Pre-lung allocation score (LAS) incidence of PGD has been reported as low as 10.7% (1). Post-LAS incidence of any PGD grade has been reported as high as 80% with severe PGD (grade 3) occurring 16–32% in the first 72 hours after reperfusion (2-5). The noted increase in part represents increasing recognition of the syndrome after standardization of the definition of PGD.

Definition

Since the initial consensus statement on PGD was first published in 2005 by the International Society for Heart and Lung Transplantation (6), efforts to refine the definition of PGD highlight the evolving complexity of lung transplant perioperative care. PGD is defined by severity of hypoxemia and alveolar infiltrates within the first 72 hours post-reperfusion (6). An updated 2016 consensus addressed such

issues as the increasing use of high flow oxygen, pulmonary vasodilators, and extracorporeal membranous oxygenation (ECMO) in the subsequent hours post-transplant (7). The update determined patients receiving post-transplant high flow oxygen should be graded the same as those with invasive mechanical ventilation based upon P:F ratio (7). Use of pulmonary vasodilators should not affect PGD grade and use of ECMO for indication of hypoxemia remained PGD grade 3 (7).

While the validity of PGD has been established by multiple studies (8,9), focus on the dynamic changes in PGD over time as shown by Shah and colleagues may prove utilitarian in future research (10). Phenotypes of PGD were defined by persistence of PGD grade 3 (class I), improvement of PGD grade 3 (class II), and resolution of PGD grade 3 altogether (10). Class I phenotypes of severe PGD had significantly higher overall risk of death and 90-day mortality (10). Other studies have proposed possibly collapsing PGD 0 and PGD 1 into one category due to the minimal impact mild PGD has on outcomes (11). Prior questions have been raised whether PGD determination should reflect transplant procedure type: single versus bilateral lung transplant. From a multicenter study by The Lung Transplant Outcomes Group (LTOG), transplant procedure type did not affect PGD and mortality prediction (11). Based upon recent revisions in ARDS definitions, some have suggested possibly delineating very severe PGD with P:F ratio <100 but so inclusion of this category did not add to overall validity, only discriminatory for early 30-day mortality (11).

Outcomes

Multiple studies have established an association of PGD with both 90-day and 1-year mortality (1,2,5). Specifically, PGD grade 3 has shown worse long-term survival and worse bronchiolitis obliterans syndrome (BOS)-free survival (12). Severity of PGD directly relates to an increase in relative risk of BOS (4). The increased risk of BOS associated with PGD does not appear to be mediated by acute rejection (4). PGD propagates inflammation which in turn increases the immunogenicity of the allograft. Bharat *et al.* showed that those with PGD went on to have significantly higher development of class II donor specific human leukocyte antigen (HLA) antibodies at 5 years post-transplant (13).

Outside of survival and BOS, studies are limited regarding other long-term outcomes of severe PGD such as quality of life. In one study 1-year survivors of PGD were significantly less likely to achieve a normal 6-minute walk test compared to those without PGD (3). Contradicting results were found in another study that found no significant difference after one year in both 6-minute walk test and cardiopulmonary exercise testing between those with or without severe PGD (14). Studies looking at post-lung transplant quality of life lacked power to examine for association of PGD with cognitive impairment but did identify risk factors for PGD such as prolonged graft ischemic time and cardiopulmonary bypass as also risk factors for cognitive dysfunction (15).

Pathophysiology

Various chemokines have been studied in human and animal models to try to understand the pathophysiology of PGD. Much focus has been on the role of innate immunity while adaptive immunity is also being recognized to have a potential role in the pathogenesis of PGD. Ischemia reperfusion injury is thought to take place over two phases with the activation of donor macrophages followed by subsequent recipient neutrophil infiltration (16,17). Differences in donor innate lymphoid cell (ILC) subsets may predispose to PGD at reperfusion. Higher donor ILC-1 populations before reperfusion appeared to be protective against PGD development while increase is post-reperfusion ILC-2 correlated with PGD (18). Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-1β have been implicated in the first phase of the pathway in increasing inflammation and neutrophil recruitment (19,20).

Toll-like receptors (TLRs) activate the innate immune response by identification of bacteria, viruses, and parasites and are thought to also have a role in PGD. Cell death that occurs at reperfusion triggers TLR4 that then goes on to release inflammatory cytokines and recruit other innate immune system players that go on to effect allograft rejection (21). Murine models of lung ischemia reperfusion injury with TLR4 knockouts resulted in significantly decreased markers of lung injury and vascular permeability (22). This is supported by recent findings that recipient variants in Toll interacting protein (TOLLIP), a regulator of TLR, had statistically significant increased risk for PGD (23). Genetic variants in this pathway may be the link that connects why those with PGD are more likely to go on to develop BOS (21).

IL-8 is a chemokine known to aid in activation and migration of neutrophils. A rise in IL-8 immediate after

reperfusion has been shown in human lung transplants as well as an inverse relationship with P:F ratio in the first 24 hours post-transplant (24). This corresponds with the influx of neutrophils into the transplanted lung after reperfusion (16,17). Aside from neutrophils themselves, neutrophil extracellular traps (NETs) are extracellular fibrous networks of neutrophil DNA and protein that have been shown to be associated with multiple disease processes including the development of PGD (25,26). These studies highlight NETs as potential targets for future therapies for prevention of PGD.

Activated complement could promote ongoing inflammation and promote capillary leak in the transplanted lung. Results have shown that changes in specific complement levels pre-operatively to 24 hours post-reperfusion are significantly associated with development of PGD (27). Lung restricted antigens such as collagen type V have been of particular focus for understanding the role of pre-formed antibodies (28,29). Complement deposition may also occur as part of humoral immunity's role in development of PGD. Due to evidence of complement deposition in post-transplant tissue samples, it is thought that these self-antibodies bind to the transplanted lung and trigger complement activation cascades (28). Evidence for a role of humoral immunity role from the LTOG group found that all subjects that converted from seronegative to seropositive for antibodies against lung restricted antigen collagen type V went on to develop severe PGD (30). Pre-transplant recipients with increased pre-formed self-antibodies have higher risk for PGD compared to those without self-antibodies pre-transplant (28).

Other studies have highlighted the potential role of epithelial cell injury activating the coagulation and fibrinolysis cascade in pathogenesis of PGD. Particular focus has been given to type I alveolar epithelial cell injury in the evolution of PGD, specifically the receptor for advanced glycation end products (RAGE) which has been found to be high both in bronchioalveolar lavage fluid and plasma of those with acute lung injury (31). For severe PGD, serum RAGE levels were found to be higher than in those with non-PGD groups (32). Another marker of epithelial injury, intercellular adhesion molecule-1 (ICAM-1), has been shown to be elevated in the plasma of those with severe PGD compared to those without PGD independent of other clinical risk factors (33). Other serum markers that have been found to coincide with PGD3 include elevated type I plasminogen activator inhibitor (PAI-1), elevated Clara cell secretory protein, and low protein C (34-36). With regards to protein C, this appears to be a difference only found after reperfusion injury with pre-operative levels being similar between severe PGD and non-PGD groups (34).

Donor risk factors

Pre-LAS studies have suggested that donor smoking history, traumatic brain injury as donor cause of death, and older age donor are associated with increased risk of PGD (1,37,38). One single center study identified donor female gender, donor African American ethnicity, and donor age <21 years also as independent risk factors for PGD (39). In contrast, another earlier study did not find that donor age independently influenced survival unless combined with prolonged organ ischemic time (40). Since the implementation of LAS, other studies have not detected significant association between donor age and PGD risk, though there was some association with extremes of age (youngest donors <18 years and oldest donors >65 years) (41). One single center study examined donors over age 60 and noted no significant difference in PGD and 30-day mortality (42). Another retrospective study did not find significant differences in PGD, 30-day mortality, or 3-year survival among donors grouped by age >70, 60–69, and <60 years (43).

Multicenter trials performed since the implementation of LAS demonstrated increased odds of PGD grade 3 with history of any donor smoking (5). A single center study showed a significant difference in short-term survival for those with significant donor smoking but no significant effect on long-term survival (44). Though data may be limited by lack of accurate reporting, one study has found no difference in severe PGD and other post-transplant outcomes between history of donor cannabis smoking and control (45). Although a multicenter registry study showed moderately inferior survival outcomes for recipients of donors with a positive smoking history versus negative smoking history, overall survival for those recipients would have been worse if they had remained on the waitlist instead (46). Overall, accepting donors with some smoking history will more likely benefit potential transplant recipients than risking potential death on the waitlist.

Donor pulmonary embolism (PE) represents a potential risk factor for PGD but studies are limited. A study utilizing exploratory flush for macroscopic emboli prior to implantation showed a 38% incidence of donor PE (47). Those with donor PE despite flush removal prior to implantation had worse PGD, longer intubation

duration post-operatively, and longer ICU stays (47). A more recent study examined results of utilizing donors who had primary diagnosis of acute PE and found similar incidences of PGD and similar overall survival (48).

Given limited donor availability and a growing waitlist, there has been a push to revisit whether use of organs that would have been declined in the past could potentially result in acceptable post-transplant outcomes. Protocols to increase the donor lung pool have not been shown to increase the incidence of severe PGD as well as not negatively affected early mortality rates (49). Standard criteria donors traditionally were considered those with age <55 years, P:F ratio >300, no infiltrates on chest imaging, no chest trauma, <20-year tobacco history, and no history of aspiration (50). There are conflicting results of whether or not extended criteria donors (ECD) have higher incidence of PGD grade 3 but most agree that longer term survival is comparable to standard criteria donors (51,52). Donors after circulatory death (DCD) were included in the ECD analysis as well as examined as a sub-analysis and showed increased severe PGD at 24 and 72 hours but similar long-term outcomes when compared to standard donors (52). Specifically looking at donors with P:F ratio <300, a recent study did not demonstrate difference though the incidence of PGD in their study overall was lower than generally reported (53).

In trying to understand the donor's role in development of PGD, Fisher *et al.* examined pre-procurement lungs from donors with brain death and found that prior to transplantation, donor bronchioalveolar lavage fluid had significantly higher levels of IL-8 in those that would go on to develop severe PGD after transplant (54). Another study looked to identify donor lung markers that could early complications such as PGD and 30-day mortality and identified the ration of IL-6/IL-10 to be most predictive, with IL-6 being higher risk and IL-10 being protective (55). This highlights the potential in targeting reduction in inflammation in the donor lung before transplantation as a way to reduce incidence of severe PGD as well as potential objective evaluation of ECD lungs before implantation.

Recipient risk factors

Significant recipient risk factors for PGD include recipient female gender, obesity, diagnosis primary pulmonary hypertension, diagnosis sarcoidosis and idiopathic pulmonary fibrosis (IPF) (1,3,5,39,56,57). Increasing recipient pulmonary arterial pressure increases risk of PGD (2,58). Pre-transplant evaluation of potential lung recipients generally include cardiac evaluation by transthoracic echocardiogram and right heart catheterization. One study established that evidence of high left ventricular diastolic dysfunction as measured by the ratio of early mitral inflow to diastolic mitral annular velocity was a significant risk factor for PGD as well as increased risk of death in the first year after transplant (59). Another study confirmed this invasively by demonstrating elevated left ventricular diastolic function on pre-transplant heart catheterization as a risk factor for severe PGD (60). It is thought that this increased back pressure from the left ventricle may contribute to PGD by means of increasing pulmonary edema.

Obesity is recognized as a significant recipient risk factor for PGD with dose-dependent increase in risk with relative increases in body mass index (61). To better understand how body composition relates to risk for PGD, a study utilized computer tomography to quantify subcutaneous and visceral adipose tissue by thoracic and abdominal location (62). No significant relationship was found between visceral adipose tissue and PGD but doubling of subcutaneous abdominal adipose tissue was significantly associated with a two-fold increase in PGD risk (62).

Genetic variations among recipients related to the pathogenesis of PGD are a focus of interest for understanding why some recipients develop severe PGD and some do not. For example, certain TLR4 polymorphisms have been associated with a decrease risk of PGD (63). Other genetic analysis studies have confirmed the role of TLR polymorphisms in development of PGD. This study also identified polymorphisms of nucleotide-binding oligomerization domain-like receptors (NLRs) and other potential variants involved in the PGD pathway (64). Other variants such as polymorphisms for PTX-3 are associated with increased PTX-3 levels and increased PGD (65). High PTX-3 levels were associated with PGD in IPF recipients but not chronic obstructive pulmonary disease (COPD) recipients which may explain why IPF is a risk factor for PGD (66). Overall, future research in understanding recipient genetic variation for risk for PGD may provide potential targets for development of preventative therapeutics.

Other risk factors

A variety or perioperative risk factors have been identified for PGD. Intraoperative use of cardiopulmonary bypass dramatically increases risk of PGD grade 3 (1,4,5) and

is overall associated with worse outcomes after lung transplant. Increased intraoperative red blood cell transfusion also increases risk of persistent PGD grade 3 over first 72 hours (10). The mechanism by which these intraoperative factors may affect PGD may be explained by increasing epithelial cell injury. Correlating with this increased risk for severe PGD, transplant recipients who had cardiopulmonary bypass or high volumes of blood transfused intraoperatively had significantly higher serum RAGE levels than those who did not (32). Cell free hemoglobin is notably elevated pre-operatively in all lung transplant recipients but rises markedly in those who undergo cardiopulmonary bypass and higher levels are associated with PGD (67). Having a FIO_2 >40 mmHg at reperfusion enhanced the association between elevated cell free hemoglobin levels and PGD risk (67).

Donor and recipient lung size mismatch has also been examined as a potential risk factor for PGD. A single center study found that undersized donor lungs were significantly associated with development of PGD (68). Eberlein and colleagues went on to confirm this finding in a multicenter study that showed oversize donor total lung capacity relative to the recipient was associated with lower odds of PGD (69). This association did not prove to be significant when adjustment was made for diagnosis of COPD (69).

Treatment

Use of perioperative pulmonary vasodilator therapy for lung transplantation is a common practice at many transplant centers. Particularly for inhaled nitric oxide, there has been some concern about insufficient evidence supporting sufficient benefit to warrant the high cost as well as no data guiding the optimal timing of use. An early small, single center study suggested a decreased incidence of PGD and decreased 2-month mortality with the use of inhaled nitric oxide and pentoxifylline at time of reperfusion (70). Another study attempted to evaluate IL-8 levels in BAL fluid between groups that received inhaled nitric oxide the first 30 minutes of reperfusion versus not and found no significant difference (71). Of note, in that same study, 80% of the control group would go on to receive inhaled nitric oxide at a later time point dependent upon decision-making of the provider (71). A larger, blinded, randomized control trial administered inhaled nitric oxide to the treatment group at reperfusion until 6 hours post-op (at which point care at the discretion of the provider) (72). In that trial no significant difference was noted in the incidence of PGD, time to successful extubation, or 30-day mortality between those that had received inhaled nitric oxide and those who had not (72). A more recent single center administered inhaled nitric oxide the first 48 hours after transplant and found significantly lower incidence PGD, lower IL-8 and IL-10 in blood and bronchoalveolar lavage (BAL) at various time points during the first 48 hours post-reperfusion (73). Overall, there have been conflicting results regarding the utility of inhaled nitric oxide in attenuating PGD suggesting larger, multicenter studies are warranted.

Though there are not standard protocols for use, multiple centers have utilized ECMO as a means of support post-transplant for severe PGD. One single center study reported 56% survival at 30 days with use of ECMO (74). Other more recent single center studies showed improved 30-day survival of 74–82% in their ECMO group thought to be attributed to improvement in ECMO technology (75,76). With improvement in ECMO technology, a more recent study of ECMO utilized post-transplant for PGD, while it still showed higher 30-day mortality in the ECMO group versus non-ECMO group, appeared to have comparable survival after 30 days (77). Other post-transplant outcomes such as BOS-free survival and acute rejection episodes appear to be similar between ECMO and non-ECMO groups (76). However, the same study did find that overall peak lung function after transplant was significantly lower for those requiring ECMO after lung transplant (76). Overall, while not ideal, ECMO for severe PGD after transplant is an acceptable support therapy until alternative treatments are achieved.

Repeat lung transplantation is not recommended as treatment in cases of persistent severe PGD. A single center study found that only 34.8% of those who underwent retransplant for PGD attained 1-year survival (78). Registry studies of retransplant overall have also confirmed that early lung retransplant (considered <90 days from initial lung transplant) results in poor outcomes (79,80).

Ex vivo lung perfusion (EVLP)

In the last decade, interest in EVLP technology as a potential way to increase the available donor pool has grown. Initial non-randomized studies showed that use of EVLP lungs did not significantly increase the incidence of PGD when compared to usual lung transplantation while the number of useable donor lungs increased by 15% (81). Another study has shown that EVLP can be used safely to extend cold ischemic time to greater than 12 hours without

an increase in incidence of PGD (82). Aside from potentially increasing the available donor pool, EVLP holds a lot of potential for future research and treatment applications. For example, Wang and colleagues have shown promise of lung reconditioning with 3-aminobenzamide during EVLP in an animal model with post-reperfusion improvements in inflammation and edema (83). Another animal study by Nakajima and colleagues showed application of mesenchymal stromal therapy during EVLP attenuated ischemic injury in donor lungs subjected to prolonged cold ischemic time (84). A new frontier in lung transplant due to EVLP research will likely revolutionize the practice in the coming decades.

Future directions

Future revisions of the definition of PGD may include combining PGD grade 0 and 1 based upon results of Cantu and colleagues (11). Other future directions include further study regarding the use and timing of ECMO and pulmonary vasodilators given the high costs and limited guidelines. This may be difficult due to varying center practice and so multicenter studies are needed. With growing research in the utility of EVLP, the development of preventative therapies for PGD may be realistic in the coming decades. Development of pre-procurement donor lung tissue analysis also hold the potential to improve prediction of PGD in the near future (85).

Conclusions

PGD remains an important outcome in lung transplant and the evolution of its definition will serve to improve its utility in research. Ongoing research to continue to understand the pathways that lead to the development of PGD will open up opportunities for development of preventative interventions. Expansion of EVLP technology has the potential to also serve as a way to both improve research techniques as well as deliver future therapeutics. While definitive solutions for PGD may continue to evade the lung transplant community for now, the future is hopeful.

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