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Report of the ISHLT Working Group on primary lung graft dysfunction Part IV: Prevention and treatment: A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation

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Dysfunction of the pulmonary allograft with impaired oxygenation and radiographic opacities consistent with pulmonary edema occurs in up to 50% of lung transplant (LTx) recipients.[1] In 2005, 4 severity grades of primary graft dysfunction (PGD 0, 1, 2 and 3) were defined by a working group within the International Society for Heart and Lung Transplantation (ISHLT).[1] In most cases, the injury is mild and transient, but in 25% to 30% of cases it can result in severe hypoxemia with a partial pressure of oxygen/fraction of inspired oxygen ratio (PaO_2/FIO_2) of <200 mm Hg (PGD 3) within the first 72 hours (T0 to T72) after LTx.[2,3]

Despite advances in our understanding of donor and recipient risk factors, donor-recipient matching, organ preservation, surgical techniques and peri-operative care, PGD still accounts for significant morbidity and mortality after LTx. This Consensus Statement on prevention and treatment of PGD aims to update the previous publication from 2005[4] by reviewing published evidence on novel strategies for reducing the incidence of PGD and for attenuating its severity once developed, in order to mitigate both short- and long-term PGD-related morbidity and mortality.

Prevention of PGD

Potential strategies to prevent and minimize the development and severity of PGD include: (1) optimizing donor

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and recipient selection, donor–recipient matching and management of donors and recipients pre-operatively; (2) improving lung preservation and storage techniques; and (3) improving lung implantation and reperfusion techniques, all based on currently known PGD risk factors.

Donors and recipients

Donor selection

Lungs are fragile and more sensitive to trauma compared with other organs. They may be acutely injured in the hours before and after brain death. This results from direct trauma due to: contusion; the resuscitation maneuver utilized; neurogenic edema; pulmonary emboli with thrombi or fat; aspiration of blood or gastric contents with infection; or ventilator-associated trauma and pneumonia. Any or all of these insults make lungs less suitable for transplantation compared with kidney and liver.[5,6] As a result, only 10% to 15% of cadaveric multi-organ donors provide lungs believed to be suitable for transplantation according to criteria that were defined during the early days of successful LTx.[7]

Efforts to expand the donor pool by transplanting extended-criteria donor (ECD) lungs have occurred worldwide.[8] Most reports demonstrate equivalent outcomes after ECD LTx with regard to PGD incidence, early and late outcomes and freedom from bronchiolitis obliterans syndrome (BOS). Three studies,[8–10] however, have reported a higher incidence of PGD 3, with increased mortality in 2 studies.[9,10] On the other hand, excluding these donors based solely on inherent donor risk factors, such as older age or considerable smoking history, may increase waitlist mortality, while the outcome for the great majority of recipients will still be much better than having not received a transplant.[11–13] On balance, caution and clinical judgment are warranted when using ECD donor lungs with more than 1 extended criterion.[10]

Lungs recovered from controlled donors after circulatory death (DCD) are increasingly being transplanted, mainly in Australia, Canada and some European countries (including Belgium, The Netherlands, Spain, Switzerland, and the UK). In several institutional reports, early and late survival rates were comparable after DCD LTx and conventional donors after brain death (DBD) LTx. This was confirmed recently both in an analysis from the DCD Registry[14] of the ISHLT and in a meta-analysis of 11 reported observational cohort studies.[15] Five studies reported on PGD data for DCD and DBD cohorts. None of these reported significant differences in PGD rates between DCD and DBD cohorts. Also, in a pooled analysis of "controlled" (Maastricht Class III or IV) DCD LTx, there was no difference in PGD rates between DCD and DBD recipients.[15] However, in the Madrid series, the incidence of PGD 3 in lung recipients from "uncontrolled" (Maastricht Class I or II) DCDs was reported to be as high as 38%, with serious impact on early- and mid-term mortality.[16] Therefore, pre-transplant evaluation of Maastricht Class I or II donor lungs with ex-vivo lung perfusion (EVLP) before LTx is now recommended by the Madrid group.[17]

Current evaluation of donor lung quality with gas exchange, chest radiograph and bronchoscopy is often difficult and quite subjective. Whenever possible, lungs should be inspected at the donor hospital. Gas exchange should be re-evaluated with the chest open and lungs fully ventilated. It is hoped that, in the near future, biomarkers correlating with (non-apparent) donor lung injury as well as reassessment with EVLP will help to better differentiate pulmonary allografts that should be declined or first treated, either in the donor before retrieval or during ex-vivo reconditioning.

Donor management

Donor management should be considered as a continuation of critical care after confirmation of brain death, with a shift in focus toward optimal continued functioning of individual organs.[18] Comprehensive donor management by qualified personnel based on protocols will increase the quantity and quality of transplantable organs.[19,20]

A systematic approach to respiratory management should be followed—in addition to hemodynamic management, hormonal resuscitation, electrolytes and fluid control and body temperature maintenance—in order to maximize the number of suitable donor lungs. In the past, respiratory management protocols used a non-protective ventilation strategy based on a tidal volume (TV) of 10 to 15 ml/kg body weight.[21] More recent approaches to optimize lung recovery include: alveolar recruitment using high levels of positive end-expiratory pressure (PEEP) (15 cmH_2O); inspiratory pressures of 25 cmH_2O; bronchoscopy to assess and minimize respiratory secretions; 30° head elevation; and endotracheal cuff pressures of 25 cmH_2O to limit aspiration.[22,23] After reporting that ventilation with higher TV was an independent risk factor for the development of acute lung injury,[24] Mascia et al were the first to prospectively study the impact of a new protective ventilation strategy on the number of lung donors.[25] This ventilation strategy is characterized by smaller TV (6 to 8 ml/kg predicted body weight) and lower PEEP (8 to 10 cmH_2O), continuous positive airway pressure during the apnea test and recruitment maneuvers, and is in accordance with the current standard of care for patients with acute respiratory distress syndrome (ARDS).[26] These different strategies were implemented in a general protocol that included: low TV (8 ml/kg); low PEEP (8 to 10 cmH_2O); recruitment maneuvers (PEEP of 15 to 18 cm H_2O); fluid restriction (targeted central venous pressure 6 to 8 mm Hg and extravascular lung water <10 ml/kg); use of diuretic, if necessary; addition of methylprednisone (15 mg/kg body weight); and thyroid supplementation in patients on inotropes. This protocol improved lung utilization without jeopardizing the acceptance rate for kidney grafts.[27] In a further study by Minambres et al, comparing 2 study periods before and after implementing an intensive lung donor management protocol, the rate of lung DBDs increased

significantly from 20.1% to 50%, thus quadrupling the total number of pulmonary grafts retrieved and patients receiving a lung transplant.[28] Of note, no differences were observed in early recipient survival or in the rate of PGD 3.

In a placebo-controlled, randomized trial, thyroid hormone alone or in combination with corticosteroids had no effect on donor lung function or yield, whereas steroids reduced progressive lung water accumulation.[29] The BOLD study, a randomized, placebo-controlled trial, evaluated the effect of nebulized albuterol on pulmonary edema, but failed to demonstrate any differences in donor oxygenation or lung utilization.[30]

Recipient selection

Recipient selection criteria for LTx were recently revisited by an ISHLT Pulmonary Council working group.[31] Since the previous publication in 2005,[32] additional studies examining recipient-related risk factors have consistently reported an association of PGD with pre-transplant diagnosis (idiopathic pulmonary fibrosis, sarcoidosis and primary pulmonary hypertension); elevated pulmonary arterial pressure; and higher body mass index.[2,33–38] Ongoing studies examining PGD mechanisms could lead to advances in the prevention or early treatment of PGD in patients with an increased risk.

Donor and recipient matching

Donor–recipient matching in LTx is usually directed by blood group (identity or compatibility) and predicted total lung capacity (pTLC) based on height, age and gender. Other donor–recipient characteristics, such as cytomegalovirus serology (+/–), gender (male/female) and age, are often ignored. The impact of donor-recipient mismatch for all these variables and their combinations on PGD occurrence has not been well investigated.[39]

In several (single-center, multicenter, registry) studies reported by Eberlein et al, a clear correlation was found between lung size mismatch and PGD. In all studies, recipients of undersized organs (donor/recipient pTLC $\leq$1.0) had an increased PGD risk, whereas those with oversized lungs (donor/recipient pTLC $>$1.0) had a reduced risk.[40–42] This distinction was most apparent in patients without chronic obstructive pulmonary disease (COPD).[40] In addition, the post-transplant TV should be appropriate for the donor pTLC and not the recipient pTLC; otherwise, ventilation-induced lung injury with capillary leak may lead to clinical PGD.[43] Moreover, the potential for detrimental hyperinflation with application of negative pleural pressure to undersized lung grafts has been described.[44] On the other hand, delayed chest closure is advised in recipients with severely oversized donor lungs to avoid hemodynamic disturbances by graft compression of the heart early after LTx.[45] An oversized allograft was associated with improved post-transplant survival for idiopathic pulmonary arterial hypertension.[46] Size mismatch was also associated with long-term pulmonary allograft function and BOS, in favor of recipients with oversized lungs.[47] In summary, incorporating the pTLC ratio into the method of lung allocation and post-transplant management could improve outcomes after LTx.

Donor–recipient matching for gender in organ transplantation is usually not considered important and so all 4 gender combinations may be possible. Few reports, mostly single-center studies with limited sample size focused on the impact of gender matching on outcome after LTx, but not specifically in relation to PGD. These studies reported a conflicting impact of gender mismatching on early and late survival and BOS.[39,48–55] In the largest study (n = 9,651) using ISHLT Registry data, Sato et al found that the combination of female donor to male recipient was associated with a higher 90-day mortality and lower overall survival, whereas female donor to female recipient was associated with the best overall survival, after adjusting for size mismatch and diagnosis.[51] Three other studies with high patient numbers reported similar conclusions.[39,49,53] It remains an open question whether donor-recipient gender mismatch is an independent risk factor for early mortality after LTx,[51] or whether worse survival in the female donor/male recipient combination is confounded by size mismatch, with more frequent use of undersized female donor lungs into male recipients.[39,40,53]

In addition to matching of demographic variables, greater attention should be given to balancing known PGD risk factors in donor and recipient. Caution and clinical judgment are still needed when matching ECD lungs to high-risk recipients, especially recipients with pulmonary hypertension.[9,56,57] Given the complexity of the interaction of multiple donor and recipient risk factors, algorithms that aid donor-recipient matching should be developed, with the aim of reducing the incidence of PGD.

Risk stratification of patients before LTx is important for several reasons. First, better identification of higher and lower risk recipient groups may allow the care team to better prepare for the likelihood of PGD development. Second, improved pre-operative prediction may facilitate safer expansion of the donor pool by characterizing lower risk recipient groups. Third, identification of higher risk recipient groups can facilitate clinical trials aimed at reducing PGD by investigating therapeutic interventions before and/or immediately after LTx. In this regard, a study by the Lung Transplant Outcomes Group produced valid estimates of PGD risk using readily available clinical variables.[58]

Donor lung preservation and storage

No large, prospective, randomized trials related to lung preservation have been performed until recently. Thus, the evidence supporting the practice, as just described, is the best available and is primarily based on findings from laboratory research and single- or multicenter cohort studies performed over the last 5 decades.[59–61] The most widely accepted and utilized conditions for lung flush and storage can be summarized as follows: preservation solution:

extracellular-type; flush volume: 60 ml/kg antegrade and 4 × 250 ml retrograde via the pulmonary veins; flush and storage temperature: 4°C; pulmonary artery flush pressure: <30 cmH_2O; route of flush: antegrade + retrograde; oxygen concentration before storage: FIO_2 0.3 to 0.5; cold ischemic time: preferably <6 to 8 hours.

The following sub-sections provide updated information regarding the conditions for optimizing lung preservation and storage, including the potential role of EVLP, based on laboratory and clinical evidence since development of the 2005 ISHLT PGD definition.[1]

Preservation solutions

No large, randomized trials are available to demonstrate the superiority in terms of outcome of one preservation solution over another. Four published clinical reports from different institutions have compared post-transplant outcomes with various preservation solutions. In a study using UNOS data between 2005 and 2008, Perfadex solution was found to be superior to University of Wisconsin solution in high-risk lung transplant recipients, with lung allocation scores (LAS) of >37.8 (1-year survival 81.5% vs 73.5%, respectively; $p = 0.02$).[62] Marasco and colleagues, in a multivariable analysis with propensity score matching, compared the impact of 3 preservation solutions (Euro-Collins, Papworth and Perfadex) on outcomes in 310 lung transplant recipients.[63] Papworth solution was associated with significantly higher mortality, whereas Perfadex was associated with a lower PGD incidence at T48. Data from the UK Cardiothoracic Transplant Audit were analyzed for possible differences among current lung preservation techniques.[64] Between 1995 and 2003, 681 lung transplants were preserved with either Euro-Collins solution ($n = 284$), blood albumin ($n = 139$), core cooling ($n = 107$) or low-potassium dextran solution ($n = 151$). There was a significantly increased use of low-potassium dextran solution over time. Risk-adjusted survival was similar across the groups and was not affected by ischemic time. Survival rates at 3 years and freedom from death caused by PGD were highest in the low-potassium dextran group and lowest in the blood albumin group (62% vs 49%, and 95% vs 91%, respectively). The Hannover group recently reported their experience with 2 extracellular-type preservation solutions, comparing historical cohorts: Perfadex ($n = 209$) from 2002 to 2005 vs Celsior ($n = 208$) from 2005 to 2009.[65] Overall 3-year survival was comparable (66.5% vs 72.0%, respectively; $p = 0.25$), with significantly longer ischemic times in the Celsior cohort (355 ± 105 minutes vs 436 ± 139 minutes; $p < 0.001$). Patients with PGD 3 who received Perfadex had significantly lower survival rates at 1, 2 and 3 years after LTx when compared with patients who received Celsior. Freedom from BOS was also lower in the Perfadex group.[65]

Flush and storage temperature

Lungs are generally stored at 4°C. Animal experiments have shown that 10°C may be superior, presumably due to preservation of membrane sodium potassium channel function.[66] Recently, the University of Groningen group revisited the question on the best temperature for pulmonary flush and storage. In a rat lung transplant model after 24 hours of inflated storage, the authors found that room temperature flushing, followed by storage on ice, provided the best method for lung graft preservation.[67]

Route of flush

Antegrade flush through the pulmonary artery has been standard practice since the first lung transplants were performed in the 1980s. A subsequent retrograde flush through the veins was found to have additive benefit,[68,69] and hence has been adopted by most as standard practice. Its beneficial effect may be related to better preservation of the bronchial tree by flushing the bronchopulmonary collaterals and by removing small clots and debris from the pulmonary arterial tree. Gohrbandt et al compared antegrade flush only ($n = 173$) vs retrograde flush only ($n = 36$) in a group of 209 Hannover recipients with lungs preserved using Perfadex.[70] PGD 3 was comparable between groups at T0 to T48, but significantly higher in the retrograde group at T72 (2.2% vs 14.8%, respectively; $p < 0.05$). Bronchial dehiscence occurred more frequently in the retrograde-only group (0.6% vs 5.6%, respectively; not statistically significant [NS]), whereas bronchial stenosis occurred more often in the antegrade-only group (24.9% vs 13.9%, respectively [NS]). Overall survival and BOS-free survival were similar.[70]

Tolerable cold ischemic time

Presently, most teams still tend to limit the ischemic times to <8 hours with extracellular-type solutions, although successful outcomes have been reported with longer times. Thabut et al, in a large French multicenter retrospective study, examined the impact of graft ischemic time on early and late outcomes in 752 patients after all types of LTx over a 12-year period.[71] Mean graft ischemic time was 246 ± 96 minutes (range 50 to 660 minutes). After adjustment for 11 potential confounders, graft ischemic time was associated with early PGD (PaO_2/FIO_2 at T0 and T6) and with long-term survival in patients undergoing single or double LTx, but not in patients undergoing heart-lung transplantation. The hazard ratio for death with longer ischemic times increased sharply after 330 minutes, and these results were unaffected by the preservation fluid used (intracellular-type vs extracellular-type). In a recent study based on a large data set from UNOS, however, prolonged (>6 hours) cold ischemic time did not impact survival at 1 and 5 years after LTx and was also not a negative predictor of primary graft failure.[72]

Using a porcine left single-LTx model, University of Toronto investigators examined the effect of a second cold ischemic period on allograft function, after an initial 10-hour period at 4°C followed by 6 hours of EVLP.[73] No differences in allograft parameters were observed at 4 hours

post-transplant between animals receiving lungs with a second 2-hour vs 10-hour cold ischemic period after EVLP. Oxygenation in both groups was superior to that of recipients of lungs preserved at 4°C for 24 hours without EVLP. These findings, if confirmed, may help to extend lung preservation time to >18 hours and may redefine the logistics of transplantation.[74]

Cold static storage vs warm preservation with EVLP

Cold pulmonary flush and static storage is currently the clinical standard for lung preservation, with the intention of lung protection by slowing cell metabolism to prevent cell death and organ deterioration.[59–61] Currently, normothermic dynamic preservation with the aid of ex-vivo perfusion is being investigated for all solid organs, including the lung.[75–79]

The modern success of prolonged (12 hours) EVLP without edema formation is in part due to improvements in technology and in part due to the use of a buffered, extracellular solution with an optimal colloid osmotic pressure.[80] In a porcine LTx study at the University of Toronto, ongoing lung injury after 12 hours of cold storage was prevented when followed by 12-hour normothermic EVLP compared with a control group with 24 hours of cold storage.[81] A prospective, international, multicenter, non-inferiority clinical trial randomized 320 bilateral, standard-criteria donor lung recipients between cold storage and immediate normothermic portable ex-vivo machine preservation with OCS Lung (Transmedics, Inc., Andover, MA) (Inspire trial: Clinical Trials.gov NCT 01630434).[82] The final results were presented at the 17th Congress of the European Society for Organ Transplantation, Brussels, Belgium.[83] In an effort to answer the question as to whether *all* donor lungs should be treated with a period of normothermic EVLP, a prospective, single-center clinical trial was conducted by the Vienna lung transplant team. They randomized 80 patients to transplantation directly after standard cold preservation with Perfadex or cold preservation plus 4 hours with normothermic in-hospital EVLP, using the Toronto technique. There were no statistically significant outcome differences demonstrable between groups.[84]

Ex-vivo methods to evaluate and recondition lungs

Unrecognized injury to the donor lung may become apparent during EVLP, allowing irrecoverably injured donor lungs with deteriorating graft function during EVLP to be declined before transplantation, thus avoiding the risk of severe PGD in the recipient. The first clinical EVLP cases were reported by Steen et al from the University of Lund, both for assessment of an uncontrolled DCD lung[85] as well as for reconditioning of an unacceptable DBD lung.[86] Since then, others have reported case series with good outcomes in ECD lung recipients after EVLP resuscitation.[17,87–101] The overall lung yield after EVLP across all reported series is around 80%.[79] Studies have suggested a lower rate of PGD 3 in recipients of initially rejected lungs undergoing EVLP compared with lungs that were grafted immediately.[89,99]

The role of EVLP for assessment and reconditioning of questionable donor lungs is being investigated in several clinical trials.[79,102,103] The first clinical trial was conducted by the Toronto Lung Transplant Program. In the HELP (Human Ex-Vivo Lung Perfusion) trial, high-risk lungs, which otherwise would not be used, were assessed with EVLP.[88,89] Eighty percent of the lungs that originally did not meet acceptance criteria from both DBDs and DCDs were ultimately transplanted after EVLP and resulted in equivalent recipient outcomes compared with those of contemporary standard control donor (SCD) lungs. Rates of PGD 3 at 72 hours after transplantation were reported to be low (2% in EVLP lungs vs 8.5% in SCD lungs).[89] Other multicenter trials of EVLP for questionable lungs (NOVEL, DEVELOP, EXPAND, PERFUSIX) are ongoing and final reports are pending.[104–108]

Besides normothermic preservation and evaluation, EVLP holds great promise for treating damaged donor lungs. Ongoing research is investigating whether lungs injured by a variety of mechanisms (brain death, contusion, aspiration, infection, edema, atelectasis) can be repaired so that some of these can become transplantable. Diagnostic strategies and targeted therapies for ex-vivo delivery will need to be developed for each of these types of injury. Potential strategies include controlled perfusion and ventilation, inhaled drugs and gases, perfusate additives and gene and cell therapy.[79,103] Thus, EVLP has the potential to reduce the incidence of PGD 3 by identifying and reversing insults in the donor organ and limiting ischemia.

Lung implantation and reperfusion techniques

The ultimate outcome of a lung transplant operation has contributions related to: (i) the donor and the cause of death and associated injuries; (ii) the lung retrieval and preservation technique; (iii) the implantation procedure and finally; (iv) the recipient. Each of these phases of the transplant procedure will need to be optimized to reduce the incidence of PGD.

Cooling during implantation

Under normothermic ischemic and anoxic conditions, lung tissue cells deteriorate very rapidly, and lung adenosine triphosphate (ATP) stores are essentially depleted in 20 minutes of warm ischemia and anoxia. Cold flush preservation has been the cornerstone of organ preservation that made transplantation possible. Stored in the inflated state, the lung has a unique preservation advantage of having a source of oxygen—hence it is in a state of hypothermic aerobic preservation.[109,110] Hypothermic static flush preservation with low-potassium dextran solution (Perfadex) has utilized this strategy to provide safe, reliable extended lung preservation.

Normothermic EVLP techniques provide a unique opportunity to bring the lung back to normal temperature

to evaluate and treat the lung, but these approaches add a degree of complexity. Once the lung is taken out of the storage phase and implanted into the patient, it is atelectatic and warm and is once again vulnerable to warm, ischemic and anoxic injury. Hence, for this phase of LTx it is still recommended that the lung be kept cool. This is achieved by a terminal flush cooling after EVLP and placing the lung on a water-cooled cooling jacket in the chest for the implantation procedure. For standard cold flush-preserved lungs, the lungs are taken out of the cooler and placed on the cooling jacket. The underlying principle is centered on the use of cold when it is needed it for protection and warm when it is needed for assessment and treatment.

Intra-operative extracorporeal support

Extracorporeal support is used selectively to perform LTx. The majority of LTx operations can be performed without the use of extracorporeal support as a single-lung transplant or sequential bilateral lung transplant technique. However, if the patient has significant pulmonary hypertension or becomes unstable during the procedure (either hypotensive or hypoxic), then one should not hesitate to use extracorporeal support. Some have advocated routine use of cardiopulmonary bypass (CPB) for all transplants, but this needs to be considered in the balance of inflammation and anti-coagulation-related morbidity vs benefit of technical ease in patients that can be transplanted without CPB.[111,112] The recent trend has been to use an extracorporeal lung support (ECLS) with ECMO circuit instead of conventional CPB, as it allows for less anti-coagulation, less coagulopathy and decreased use of blood products.[113–118] In the Lung Transplant Outcomes Group study, CPB was associated with higher rates of PGD; however, planned vs emergent CPB use was not prospectively recorded.[2]

Blood and blood product use

The Transfusion-related Acute Lung Injury (TRALI) is a well-described phenomenon of inflammatory lung injury and an ARDS picture after significant transfusion of blood products. The already-injured lung (with ischemia-reperfusion injury) is vulnerable to this as an additional "hit," and therefore it is advisable to avoid blood transfusion wherever possible.[2] Furthermore, use of the cardiotomy sucker in standard CPB is also not advisable as the activated blood likely contributes to further lung injury as an extrapolation of the aforementioned concept. Use of a cell saver (also necessary for ECMO circuits) is the favored way to autotransfuse shed blood as concentrated and washed red cells are returned to the patient.

Methods to control reperfusion

The endothelial and epithelial cells in hypothermically preserved lungs have stiff cell membranes and the rapid reintroduction of pulmonary artery (PA) blood flow can inflict a significant shear stress injury to the lung. Studies have demonstrated that gradual reintroduction of blood flow over a period of 10 minutes—by slowly releasing the PA clamp, can significantly improve graft function.[119,120] If the transplant is performed on ECLS support, it is important to maintain perfusion (some ejection by the right ventricle) and ventilation to the newly implanted lung while the second lung is implanted. This avoids adding warm atelectatic ischemic injury and allows the lung to begin its recovery phase in a setting of protective ventilation and protective (low-pressure, low-flow) perfusion. Studies have reported on reperfusion with leukocyte-filtered blood[121,122] and on adding pharmacologic agents to the initial perfusate of the implanted lung.[123] Ideally, as we gain better understanding of the mechanisms of the reperfusion state, these types of interventions can be applied to specifically target known components of the injury.

Principles of protective ventilation

Ventilation of the newly implanted lung should be protective. This includes keeping the FIO_2 low during the early reperfusion period—in the range of 0.21 to 0.5. Ventilation control is usually set at the lowest pressure controlled setting to achieve a reasonable TV and a PEEP of 5 to 8 cmH_2O to assist with gradual recruitment of alveoli.[124]

Prophylactic post-operative ECLS (ECMO)

ECLS has traditionally been used as an advanced support measure for severe PGD in the early post-transplant phase (see next subsection). It is generally accepted that earlier institution of ECLS leads to improved salvage rates rather than delayed implementation.[125,126] As an extension of this, some centers have advanced the concept further to leave patients on ECLS for a period of recovery (1 to 3 days or so) when early graft dysfunction is manifest in the operating room, or even to leave patients on ECLS "prophylactically" in high-risk recipient cases, such as those with primary pulmonary hypertension.[127,128] Using ECLS as a "prevention of PGD" strategy in this fashion is somewhat surgeon- and center-specific and further study is required to determine the threshold at which ECLS could be applied as a "prophylactic" strategy to protect the newly reperfused lung in prevention of severe PGD.

Treatment of PGD

General principles of post-transplant PGD management

There is no consensus on the treatment of PGD, primarily due to a lack of appropriately powered clinical studies on the topic. However, there are many similarities between PGD and ARDS, as they are both characterized by severe hypoxemia and radiographic evidence of diffuse alveolar infiltrates.[1,129] Most transplant centers tailor their therapies for PGD based on extrapolated treatments of ARDS.[2,130]

As with ARDS, the overall goal in management of patients with PGD is to minimize oxygen toxicity and to prevent the volutrauma and barotrauma associated with mechanical ventilation.[131] Although the mainstay of therapy remains supportive care in the majority of cases of PGD, there have been data published on utilizing ECMO in patients with severe PGD to enable more effective supportive care with less toxicity to the lung allograft.[132–134]

Ventilator management

There are no clinical studies that have evaluated the various mechanical ventilation modalities in patients with PGD, but, given the radiographic and clinical similarities to ARDS,[26] many centers use lung protective ventilation (also known as low TV ventilation) with PEEP as a mainstay of therapy.[135]

Fluid management

In general, fluid restriction should be used in conjunction with lung-protective ventilation in patients with PGD. However, it is important to maintain adequate perfusion so there is less systemic cytokine release. Judicious diuresis and fluid control can be used to minimize systemic perturbations in hemodynamics while avoiding worsening capillary leak and pulmonary edema. This is typically achieved by optimizing blood counts via transfusions and using systemic inotropes and/or vasopressors. Of note, the optimal hemoglobin level post-transplant has not been determined.[4]

Pulmonary vasodilators

Nitric oxide

Preservation and reperfusion of donor lungs markedly reduces nitric oxide (NO) availability.[136] Ischemia–reperfusion injury after LTx, characterized by increased capillary permeability and the development of non-cardiogenic pulmonary edema, is thought to be a hypoxic injury resulting in alterations in inflammatory mediators followed by a decline in endogenous NO. Several experimental animal model studies have shown that administration of NO to the lung allograft results in decreased pulmonary vascular resistance as well as neutrophil adhesion and platelet aggregation.[137,138] Further experimental animal studies showed improved lung allograft function with NO treatment.[139,140] However, small, randomized clinical trials failed to show that prophylactic inhaled NO (iNO) had an impact in prevention of PGD.[141–143] A recent systematic review and meta-analysis for recipient-related clinical risk factors for PGD also found no significant association between the use of intra-operative iNO and development of PGD.[144] However, none of the trials performed have been powered to detect potentially small, but real, differences in PGD.

Similar to ARDS treatment,[145] NO may be useful in the treatment of established PGD by reducing pulmonary vasoconstriction and enhancing ventilation-perfusion matching. Although case reports exist with conflicting evidence regarding clinical outcomes, there continues to be a lack of randomized clinical studies evaluating the use of NO in the treatment of PGD after LTx.[146–149]

At this time, we cannot recommend routine prophylactic use of NO for the prevention of PGD. However, NO may be used selectively in patients with established PGD 3 showing severe hypoxemia and elevated pulmonary artery pressures as part of overall treatment program.

Prostaglandins

Prostaglandins such as PGI_2 (epoprostenol) and PGE_1 (alprostadil) play a significant role in pulmonary vasodilation and inhibition of inflammatory events such as disruption of the alveolar-capillary barrier, leukocyte adhesion and platelet aggregation.[150] These effects are mediated through cyclic adenosine monophosphate (cAMP) pathways that are disrupted with the ischemia-reperfusion injury in LTx recipients. Similar to NO, administration of prostaglandins has been shown to reduce pulmonary vascular resistance and improve oxygenation.[151–153] During transplant, administration of inhaled prostaglandins before organ procurement or after implantation has resulted in decreased inflammatory cytokines, decreased pulmonary edema, decreased pulmonary artery pressure and central venous pressure, and improved cardiac index and mixed venous oxygen saturation.[153–155] However, no studies to date have evaluated the effects of these changes on clinical PGD.

At this time, there is insufficient data to recommend the use of routine inhaled prostaglandins for the prevention of PGD after LTx, although the use of inhaled prostaglandins for severe hypoxemia or elevated pulmonary artery pressures may prove to be a useful adjunct, similar to inhaled NO.

Novel therapies for prevention and treatment of PGD

Novel therapies for PGD have focused on prevention over treatment and include surfactant, complement inhibition, platelet-activating factor antagonists, platelet and neutrophil traps, stem cells and plasmapheresis. Human studies evaluating their role in the prevention and treatment of PGD are listed in Table 1. More details on these novel therapies are given in Appendix 2.

ECMO

A subset of patients with PGD 3 has the potential to benefit from post-transplant ECMO. In most cases of PGD, optimization of conventional ventilator support allows for recovery of the injured lung. However, mechanical ventilation alone cannot achieve sufficient gas exchange in some patients with severe PGD. In such cases, the therapeutic interventions mentioned earlier may be utilized. If these therapies fail, ECMO is recommended. The general

Table 1 Summary of Human Studies Evaluating Novel Interventions for Prevention and Treatment of PGD After Lung Transplantation

Therapy	Design	Results	Author and reference no.
Surfactant: endobronchial instillation of 20 mg/kg before reperfusion	RCT: 42 recipients	Lower PGD, earlier extubation	Amital et al[189]
Surfactant: endobronchial instillation 3 to 7 days post-Tx	Case series: 5 patients	Improved P/F ratio in the setting of severe PGD	Amital et al[191]
Complement inhibition: TP-10 (10 mg/kg) before reperfusion	RCT: 59 patients	No significant difference in time on vent or ICU stay	Keshavjee et al[193]
Platelet-activating factor antagonist: 2 mg/kg and 10 mg/kg	RCT: 24 patients	Short-lived improved P/F ratio <8 hours after Tx	Wittwer et al[210]

ICU, intensive care unit; P/F, PaO_2 to FIO_2 ratio; PGD, primary graft dysfunction; RCT, randomized, controlled trial; Tx, transplant.

indication for ECMO in PGD is severe hypoxemia (PO_2/FIO_2 <100 mm Hg) not responsive to pulmonary vasodilation, with or without hypercapnia, acidosis and right ventricular dysfunction.

One of the major concerns when using ECMO in the post-transplant period has been the high incidence of complications, such as bleeding, vascular injury and neurologic deficits. According to the ARDS literature, the incidence of such complications has dramatically decreased in recent years. The main reasons for this decrease are: (1) improved device technology leading to less blood trauma and the requirement of lower anti-coagulation parameters (activated clotting time 160 to 180 seconds or activated partial thromboplastin time 1.5 to 2 times normal); (2) earlier implementation of ECMO so patients are not in multiorgan failure; and (3) broad use of venous-venous (V-V) ECMO instead of venous-arterial (V-A) ECMO. V-V ECMO can properly support the majority of patients with severe PGD, even in the setting of hemodynamic compromise. Correction of hypoxemia and acidosis with V-V ECMO and pulmonary vasodilation due to oxygenated blood perfusing the lungs often leads to rapid hemodynamic improvement, which nullifies the need for V-A ECMO. One exception to this generalization is in patients with primary pulmonary hypertension, where V-A or V-VA hybrid ECMO is often extended to the post-transplant period to protect the left ventricle from overflow and subsequent cardiogenic pulmonary edema.[127,128]

A topic of continued controversy is whether V-A ECMO can better protect the injured lungs by offloading the pulmonary circulation. Although this assumption is physiologically sound, one needs to balance the risks and benefits of such approach vs V-V ECMO. Some data also support V-V ECMO as a strategy to decrease pulmonary artery pressures (PAPs) with an average PAP decrease of 20 mm Hg after initiation.[156] Reduction of pulmonary perfusion with V-A ECMO may also lead to increased incidence of bronchial complications, as bronchial vascularization is dependent on pulmonary flow in the early post-transplant period. Other concerns with V-A ECMO include increased vascular complications from the arterial puncture site, increased neurologic complications, and need for anti-coagulation.

Exemplifying clinical practice, Bermudez and colleagues reported on a large proportion of V-A ECMO use for PGD, with survival rates of 56%, 40% and 25% at 30 days, 1 year and 5 years, respectively.[133] In contrast, Hartwig and colleagues used V-V ECMO for PGD in 6% of their transplant population with survival being substantially better than in previous reports: 30 days, 82%; 1 year, 64%; and 5 years, 49%.[134] Thus, V-V ECMO has been the growing mode of choice for extracorporeal life support in patients with severe PGD.

Taken together, these findings indicate that post-transplant ECMO is useful for supporting patients through PGD, but this population still has significantly lower long-term survival than patients without severe PGD.

Retransplantation

Less than 5% of all lung transplants performed are retransplants.[157,158] Despite improvements in overall outcomes, repeat LTx demonstrates worse overall survival than primary LTx. Early "re-do" LTx survival remains particularly hazardous, and this should remain an option of last resort for the treatment of PGD. Ideally, a patient with PGD can be managed with the more conservative measures, as described earlier in this report. This would include mechanical support such as V-V ECMO, which has proven to be an invaluable and safe mechanism for bridging patients through severe PGD. If these other means of treatment and support prove unsuccessful, then the option to retransplant the patient may be entertained. The clinical team should not take this decision lightly as it presents a tremendous challenge to resources and likely endangers another pulmonary allograft that may be more appropriately utilized in an another recipient.

The ISHLT Registry data indicate that survival after repeat LTx remains well below that of primary LTx.[157] However, the median survival after retransplantation has improved over time and, in the most recent era, has reached 3.0 years. A similar result can be seen in the UNOS registry.[159] Some of this may be due to improvements in best available care, but some of the improvements may also be secondary to implementation of the LAS in the United States and elsewhere, which more quickly triages available allografts to these patients over less ill ones. What is clear when analyzing both data sets is that the interval between

primary transplantation and retransplantation is strongly associated with survival. In the ISHLT Registry, those patients retransplanted within 1 month of the primary transplant had a median survival of <6 months. Similarly, early retransplant, <90 days after primary transplant in the USA experience, showed a hazard ratio (HR) = 2.4 compared with late retransplant and an HR = 3.1 compared with primary transplant. Likewise, in the USA, those patients specifically retransplanted for PGD had worse survival compared with those transplanted for BOS (HR = 1.63, 95% confidence interval 1.11 to 2.38), even since implementation of the LAS. Although the data would suggest that peak allograft function is attenuated in patients with severe PGD,[134] a better resource utilization strategy may be to support patients with severe PGD through the process and then perform late retransplant if necessary, when overall survival is expected to be better.

Conclusions

Dysfunction of the pulmonary allograft during the first 72 hours after LTx may be the end result of several physiologic and biochemical insults that occur during the transplantation process, namely: in the donor before and after death; during flush preservation and storage; during implantation; and after reperfusion in a specific recipient. For the best possible outcome, each of these phases of the transplant procedure will need to be optimized. There has been significant progress in the past decade in identifying donor and recipient risk factors for PGD.

Thankfully, in most patients, PGD is of mild to moderate severity, and can be managed with standard supportive therapy in the intensive care unit. In some patients, however, PGD can be severe. Many findings have been published on utilizing ECMO early in the post-transplant course to support these patients who are at significant risk for early death.

As we learn more about the mechanisms of this injury, new strategies need to be developed to specifically ameliorate each component of the injury process. Multicenter clinical trials would be helpful in determining the best management for LTx recipients with PGD. The goal of the LTx community is to reduce the risk for early death and improve early- and long-term outcome after LTx for patients afflicted with PGD at all levels of severity.

Disclosure statement

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Appendix 1. : ISHLT PGD Working Group IV

Members of the ISHLT PGD Working Group IV include: Marcelo Cypel, R. Duane Davis, Matthew G. Hartwig, Don Hayes, Jr, Steve Ivulich, Marshall I. Hertz, Shaf Keshavjee, Jasleen Kukreja, Erika Lease, Gabriel Loor, Olaf Mercier, Luca Paoletti, Jasvir Parmar, Reinaldo Rampolla, Dirk Van Raemdonck, Rajat Walia, and Keith Wille.

Appendix 2. : Novel therapies for prevention and treatment of PGD

1. Surfactant

Pulmonary surfactant is a heterogeneous, surface-active lipoprotein complex that is composed of 90% lipids (65% phosphatidylcholine) and approximately 10% serum-derived proteins, with the latter representing the 4 surfactant-associated proteins (SP-A, SP-B, SP-C and SP-D).[160,161] After synthesis by Type II pneumocytes, surfactant is secreted into the alveolar space where it forms a stable monolayer, resulting in reduced surface tension of the alveoli and stabilization during end-expiration, prevention of atelectasis and alveolar edema and an optimal surface area for gas exchange.[160,161] Clinical and experimental studies have demonstrated that ischemia, cold storage and reperfusion associated with LTx influences surfactant composition and function,[162–167] including alterations in the surfactant aggregate ratio with decreases in phosphatidylcholine and phosphatidylglycerol. These alterations correlate with a reduction in pulmonary compliance, resulting in alveolar collapse, ventilation-perfusion mismatch, pulmonary edema and decreased oxygenation.[168–170] Moreover, preliminary experimental studies and clinical experience with exogenous administration of surfactant have shown partial mitigation of these complications.[162–165,171–182]

Although exogenous surfactant appeared to be beneficial in LTx in early studies, critical questions remain that include dosing and timing of administration (e.g., at procurement vs reperfusion, or both). In an important experimental model, attenuation of lung ischemia-reperfusion injury by pre-ischemic exogenous surfactant was described through stabilizing and increasing the active endogenous intra-alveolar surfactant pool.[183] Donor lung pre-treatment with an SP-A-free surfactant agent also maintained serum NO and reduced hemodynamic disturbances, while better preserving alveolar integrity in a porcine LTx model.[170] Likewise, in another experimental model, treatment with surfactant before lung reperfusion resulted in improved lung compliance, improved oxygenation, decreased protein leakage and enhanced survival.[184,185] Again, when administered before ischemia-reperfusion injury, intratracheal surfactant application significantly reduced intra-alveolar edema and prevented atelectasis, whereas peribronchovascular edema increased and alveolar Type II cells' morphologic alterations were not influenced by surfactant treatment,[186] suggesting the benefit of exogenous surfactant is related to intra-alveolar activity. In a murine model with

exogenous surfactant being effective in both prevention and treatment of lung ischemia-reperfusion injury, Wittwer et al[187] evaluated its application at the time of flush preservation, after 4-hour ischemia and during reperfusion and found that donor lung pre-treatment with endobronchial surfactant provided optimal preservation quality compared with post-ischemic application or during reperfusion.

Several groups have undertaken research examining the benefit of exogenous surfactant in human LTx. The Hannover group performed a single-center, prospective, randomized trial in which surfactant was instilled by bronchoscopy into donor lungs before retrieval; the surfactant study group had higher phospholipids in bronchoalveolar lavage fluid and improved surfactant function based on enhanced small-to-large aggregate ratio.[188] Clinically, the patients given surfactant had a significantly higher pulmonary function 1 month after transplant, but this difference disappeared by the end of the first post-transplant year.[188] In another single-center, prospective, randomized study,[189] surfactant was delivered through a bronchoscope after establishment of bronchial anastomosis and demonstrated improved oxygenation, fewer radiographic abnormalities, lower PGD grade, reduced severe PGD rates, earlier extubation and shorter intensive care unit length of stay, along with better short-term pulmonary function outcomes. As a salvage therapy after ischemia–reperfusion injury or development of PGD in lung transplant recipients, 2 case series successfully used exogenous surfactant with significant improvement in oxygenation and resolution of radiologic infiltrates and showed excellent short-term graft function.[190,191]

For now, exogenous surfactant therapy remains as a promising therapeutic option for lung ischemia-reperfusion injury in LTx, with associated improvement in oxygenation, prevention of PGD, and optimal short-term clinical outcomes in single-center studies and case series. Although there is a lack of rigorous prospective, randomized studies, the available data suggest surfactant may best be used in a preventive, as opposed to therapeutic, manner.

2. Complement inhibition

With activation of the complement system having an important role in mediating reperfusion injury after LTx, early interference of this pathway has been examined as a potential therapeutic target to reduce lung reperfusion injury in LTx. Complement activation accelerates tissue injury directly by complement factors or indirectly by complement-mediated polymorphonuclear neutrophil activation. In a large-animal model in which C1-esterase inhibitor was infused (half the dose given 10 minutes before and the other half 10 minutes after reperfusion), reduced lung ischemia-reperfusion injury and improved pulmonary function were observed.[192] Starting in the late 1990s, experimental studies, case reports and a multicenter, randomized, double-blinded, placebo-controlled trial showed early evidence that soluble complement receptor-1 (sCR1), a complement inhibitor, may be beneficial for the treatment of PGD.[193–197] In the randomized, double-blinded, multicenter, placebo-controlled trial, where 28 patients received sCR1 and 31 received placebo before reperfusion, early outcomes were improved in the setting of 90% complement inhibition for 24 hours, with a return to normal activity by 72 hours.[193] Combining the complement inhibition of sCR1 with the leukocyte adhesion inhibition of selectin ligand sialyl Lewis X (sLeX) resulted in a significant reduction of reperfusion injury in experimental models, with no effect on graft rejection.[198,199] More recently, the role of complement-mediated microvascular injury in chronic lung allograft rejection has been under investigation.[200] In kidney transplantation, targeting complement activation in the donor after brain death improved short-term renal function after transplantation in recipients.[201] With clear evidence that complement inhibition improves early outcomes, further research is needed to determine optimal techniques of administration of these potential therapies at time of reperfusion in LTx in order to prevent PGD and potentially improve long-term outcomes.

3. Platelet-activating factor antagonists

Platelet-activating factor (PAF) is a phospholipid that is released during ischemic lung injury, so PAF antagonists were initially described as a potential adjunct for lung preservation in the early 1990s.[202–208] A PAF antagonist combined with an endothelin antagonist in an experimental model showed superior post-transplant graft function 24 hours after reperfusion compared with no treatment and each individual agent, suggesting a synergistic role.[209] A 2001 study in humans demonstrated significant improvement in alveolar-arterial oxygen differences for the first 12 hours after reperfusion and better chest X-ray score in randomly assigned patients who received low-dose ($n = 8$) and high-dose ($n = 8$) PAF antagonist in the flush solution before reperfusion, when compared with a control group ($n = 8$).[210] The investigators reported a clear benefit of the PAF antagonist in the early post-ischemic period, but the distinction dissipated after 32 hours.[210] In 1994, a single-center, randomized, double-blind trial on 29 kidney transplant recipients showed significantly less primary graft failure in donor organs treated with a PAF antagonist.[211] More recently, anti-PAF attenuated leukocyte adhesion response in an experimental model of bowel ischemia with application in small bowel transplantation resulted in improved sub-mucosal capillary flow and reduced tissue injury.[212] Although investigations on the role of PAF antagonists in LTx are not as common as they were 2 decades ago, there is enough evidence suggesting they may be useful as adjunct therapy during the early post-transplant period and thus may assist in PGD treatment. Further research is needed to better define the role of PAF antagonists in LTx.

4. Platelets and neutrophil extracellular traps

Platelets may represent a target for therapy as previous studies have highlighted a potential role in lung injury.[213]

More recently, platelet depletion in 2 mouse models of ARDS reduced the severity of lung injury and increased survival. Platelet deprivation post-operatively may not be feasible, but this effect could also be reproduced by pre-treatment with aspirin.[214–216] Interest in pre-emptive treatment with aspirin in ARDS is being explored in high-risk pre-operative patients.[215] This may potentially be translatable to LTx recipients as a preventive or therapeutic strategy.

The presence of neutrophil extracellular traps (NETs) is thought to activate epithelial cells and increase the aggregation of platelets. This observation was confirmed in both an experimental mouse model and a human study. Targeting these NETs with DNAse alone and in combination with aspirin decreased the degree of lung injury in both models.[217] One possible mechanistic explanation is the observation that delayed neutrophil apoptosis, a feature of ARDS, is decreased by aspirin, which allows for resolution of the persisting inflammation.[218]

5. Stem cells

Stem cells are considered to have potent anti-inflammatory properties, through local paracrine mechanisms, as well the tantalizing potential for local regeneration. Stem cells also have the ability to donate functioning mitochondria to injured cells. Multiple animal studies in ARDS models have demonstrated an increase in the anti-inflammatory cytokines (interleukin-8 and interleukin-1 receptor antagonists), thus ameliorating inflammation. A small-scale human EVLP study involving 4 discarded donor lungs in a protracted ischemic model suggested improvement in the inflammatory profile and histology after intratracheal administration of multipotent adult progenitor cells.[219–221] Interest in this area has grown significantly and a critical care medicine society has proposed a Phase I study, the STem Cells for ARDS Trial (START), to examine the feasibility of treatment with stem cells.[222]

6. Plasmapheresis

The presence of non-HLA antibodies has been linked to development of both PGD and BOS, particularly in cystic fibrosis and idiopathic pulmonary fibrosis patients. In a single-center retrospective study, the presence of $K_{\alpha 1}$ tubulin and collagen V auto-antibodies was associated with a significantly higher risk of PGD (88% vs 54%, $p < 0.05$) compared with control groups.[223] The possibility of reducing these antibodies with plasmapheresis may provide a novel target for at-risk populations.

7. Future developments

The intensity of injury generated by an episode of PGD suggests that multiple pathways are synchronously activated at the time of lung reperfusion. The Lung Transplant Outcomes Group has identified a series of potential therapeutic targets related to oxidant stress that were statistically related to PGD, including donor NADPH oxidase 3 (NOX3), glutathione peroxidase (GPX1) and nuclear factor (NRF-2). The GPX1 association included 3 individual loci (p-values between 0.006 and 0.049) and the NRF-2 (NFE2L2) association included 2 loci ($p = 0.03$ and 0.05).[224] Polymorphisms in the interleukin-17 and interleukin-23 receptors of the recipients were associated with an increased incidence of PGD.[225] Further elucidating the affected pathways in PGD may lead to novel therapeutic interventions.

Unfortunately, 2 large, randomized, controlled trials examining the use of β_2-agonists and statins in ARDS failed to demonstrate a benefit from either therapy.[226,227] However, it is of interest to note from observational data from the ISHLT Registry that patients on statins post-LTx have a better outcome than those not on statins.[228] Other novel therapies, including renin-angiotensin axis blockers, peroxisome proliferator agonist receptor ligands, curcumin and inhaled heparin, are currently being considered. These approaches have some supporting data in animal models, but have limited clinical data.[229]

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