Report of the ISHLT Working Group on Primary Lung Graft Dysfunction Part IV: Recipient-Related Risk Factors and Markers

Mark L. Barr, MD,[a] Steven M. Kawut, MD, MS,[b] Timothy P. Whelan, MD,[c] Reda Girgis, MD,[d] Heidi Böttcher, MD,[e] Joshua Sonett, MD,[b] Wickii Vigneswaran, MD,[f] David M. Follette, MD,[g] and Paul A. Corris, MB, FRCP[h]

Numerous studies have attempted to identify recipient-related characteristics that portend poor clinical outcomes after lung transplantation. As already covered in the previous parts of this series, a major cause of morbidity and mortality during the early post-operative period is primary graft dysfunction (PGD). Unfortunately, most studies have included small numbers of patients or have used variable or unclear definitions for PGD. PGD increases early morbidity and mortality and accounts for roughly 50% of early (30-day) deaths.[1] Therefore, risk factors for PGD are likely also risk factors for short-term morbidity or mortality, which are often better defined. In this investigation, we characterize the association of various recipient-related risk factors and markers with PGD. There are multiple potential risk factors that affect early clinical outcomes after lung transplantation, only one of which is PGD. We therefore also briefly cover other causes of early graft dysfunction and/or mortality that are part of the differential diagnosis when considering PGD. Although many of the earlier studies used a Pa_{O_2}:F_{IO_2} ratio of <150 at 24 hours and/or radiographic patterns as part of their definition of PGD, other studies used alternate definitions, often making comparisons and definitive conclusions difficult.

DEMOGRAPHICS

Existing evidence does not support an association between recipient age and the risk of PGD.[1-4] Although one study showed a younger mean age of patients with PGD versus those without, there was no adjustment for other potential confounders, such as underlying disease and use of cardiopulmonary bypass.[5] The incidence of PGD and risk factors in pediatric lung transplant recipients are also poorly defined.[6] Recipient gender (independent of the higher likelihood of sensitization from pregnancy) does not appear to affect the risk of PGD. A recent study of 255 consecutive lung transplant patients found that female recipients had an increased risk of developing PGD (odds ratio = 3.0, 95% confidence interval 1.22 to 8.12, $p = 0.009$); however, this association did not persist after adjusting for donor gender.[2] Recipient race has not been associated with the risk of PGD.[2]

CO-MORBIDITIES AND OTHER ORGAN SYSTEM DISEASES

Body Weight

Although two studies have identified obesity (body mass index [BMI] >27 to 30) as a significant risk factor for early mortality and longer intensive care unit stay, there are no specific studies of body weight and the incidence of PGD.[7,8]

Hepatic Impairment

Among 62 patients with pulmonary arterial hypertension undergoing heart–lung transplantation, the early mortality of those with a serum bilirubin >2.1 mg/dl was 58% compared with 27% for those with a level between 1 and 2 mg/dl, and 16% in those with a normal value.[9] Liver congestion from right-heart failure is common among recipients with severe pulmonary hypertension, and impaired hepatic function could independently contribute to higher mortality in this population.[10,11] The severity and etiology of the liver abnormalities likely determines this risk; mild cystic fibrosis (CF)-related liver disease does not appear to affect short-term outcomes.[12]

Renal Impairment

There are no data regarding the risk of PGD in patients with renal impairment. However, the registry of the International Society for Heart and Lung Transplantation (ISHLT) showed an association between higher pre-transplant serum creatinine concentration and 1-year mortality.[1] Hypervolemia related to impaired renal func-

From the [a]University of Southern California, Los Angeles, California; [b]Columbia University, New York, New York; [c]University of Minnesota, Minneapolis, Minnesota; [d]Johns Hopkins University, Baltimore, Maryland; [e]Deutsches Herzzentrum, Berlin, Germany; [f]Loyola University Medical Center, Maywood, Illinois; [g]University of California, Sacramento, California; and [h]Freeman Hospital, Newcastle upon Tyne, UK.

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Reprint requests: Mark L. Barr, MD, Department of Cardiothoracic Surgery, University of Southern California and Children's Hospital of Los Angeles, 1520 San Pablo Street, Suite 4300, Los Angeles, CA 90033. Telephone 323-442-5849. Fax: 323-442-5956. E-mail: mbarr@surgery.usc.edu

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tion would be expected to exacerbate the severity of pulmonary edema formation in the setting of PGD.

Left Ventricular Dysfunction

There are few data regarding pre-transplant left ventricular (LV) function and PGD. In one study, there was no significant association between pre-operative LV disease or hemodynamics and post-operative respiratory failure.[3] The presence of coronary artery disease requiring re-vascularization with normal LV function does not appear to adversely influence early outcomes.[13] Although, by definition, PGD requires the absence of a cardiogenic component, even a slightly elevated pulmonary capillary pressure could substantially contribute to this syndrome by increasing vascular hydrostatic pressure and pulmonary edema in a lung allograft with an impaired endothelial barrier.

Diabetes

A donor, but not recipient, history of diabetes was a risk factor for early mortality in the ISHLT registry,[1] but the contribution of PGD is unclear.

Immunologic Factors

Although the diagnosis of PGD requires the exclusion of hyperacute rejection, the clinical distinction between these two entities may be difficult. Moreover, immunologic factors may contribute to the pathogenesis of PGD without frank rejection. One group showed a longer median duration of post-operative mechanical ventilation in patients with panel-reactive antibodies (PRA) of >10% compared to patients without antibodies (9 days vs 1 day, respectively, $p = 0.008$).[14] Not surprisingly, the vast majority of patients with an elevated PRA were women; however, recipient gender was not incorporated in multivariate analyses. Similarly, a high incidence of early graft dysfunction has been described in recipients with low titers of donor-specific HLA antibodies detected by flow cytometry.[15] When available, pathology in these cases has occasionally documented antibody-mediated or hyperacute/accelerated rejection. No difference in PGD was noted among 36 recipients receiving an ABO blood type–compatible graft compared with 64 ABO-identical grafts.[16]

Medications

There are insufficient data to support or refute an association between medication use and PGD. Early reports have suggested a link between steroid use and airway dehiscence, but subsequent studies have failed to document this and no link has been made with PGD.[1,17–19] The use of intravenous inotropes at the time of transplant and a resting oxygen requirement were risk factors for 1-year mortality in the ISHLT registry, but it is not known whether these are related to PGD.[1]

HISTORY OF PRIOR THORACIC SURGERY/PLEURAL ADHESIONS/MECHANICAL VENTILATION

Re-transplantation

Short-term mortality is considerably increased for recipients with a second allograft, particularly those transplanted acutely for severe PGD[20] and those who are non-ambulatory and ventilator-dependent.[21] The occurrence of PGD has not been specifically documented in these reports. Among 15 recipients re-transplanted for obliterative bronchiolitis, only 2 died of PGD, suggesting that the risk of PGD is not substantially elevated.[19]

General Thoracic Procedures

A cohort of 18 recipients who had undergone earlier pleural procedures showed no difference in post-operative outcomes, including duration of mechanical ventilation, when compared to those of patients without a history of thoracic procedures.[22] Similarly, a series of 7 recipients who had undergone intrathoracic procedures had similar post-operative outcomes to those of 40 recipients without a history of thoracic surgery.[23]

Dense Pleural Adhesions

The aforementioned small series do not exclude the possibility that dense pleural adhesions and thickening, which increase the surgical trauma and intraoperative bleeding of native lung extraction, could promote the development of PGD.[24] Such an association has been reported anecdotally in sarcoidosis. The presence of mycetoma and consequent pleural reaction may increase this risk. Three of 9 patients with mycetoma died from PGD, suggesting a particularly high incidence.[25] Moreover, post-operative hemorrhage requiring re-exploration, not an infrequent occurrence in cystic fibrosis, may further exacerbate PGD.[26,27]

Lung Volume Reduction Surgery

There is no clear evidence that earlier lung volume reduction surgery (LVRS) increases the risk of PGD. However, patients who are transplanted soon after a failed LVRS appear to have an increased short-term mortality compared with recipients having a longer interval between LVRS and transplant.[28]

History of Surgery for Congenital Heart Disease

Sixty-seven percent of heart–lung transplantation recipients with Eisenmenger syndrome and a history of a prior thoracotomy require re-operation for hemorrhage.[29] This combination is associated with a 30-day mortality of 25% compared with 6% in those not requiring re-exploration. This mortality is related predominantly to intractable bleeding; however, PGD accounted for 3 of 8 early deaths in this series. A similar experience has been reported in children.[30]

MECHANICAL VENTILATION

Pre-transplant mechanical ventilation does not appear to increase the risk of PGD.[20,31,32]

UNDERLYING DISEASE

Obstructive Lung Disease

Chronic obstructive pulmonary disease (COPD) patients consistently have the lowest risk of PGD (with a reported incidence as low as 3%).[2,5,33] In one study, patients with α_1-anti-trypsin deficiency had a higher incidence of PGD (9%) and a somewhat longer duration of ventilation and intensive care unit stay compared with those of other emphysema patients. However, bilateral transplantation was also more frequent in the former group, suggesting that confounding variables other than diagnosis may account for the worse early graft function. In a smaller series, 0 of 17 patients with α_1-anti-trypsin deficiency developed PGD, compared with 7 of 42 COPD patients.[34]

Suppurative Lung Disease

The incidence of PGD in CF has been reported to range from 10% to 33%.[2,26,34] In the largest single series of 123 patients from the University of North Carolina, lethal acute graft failure occurred in 3 cases, but the overall incidence of PGD was not reported.[35]

Restrictive Lung Disease

Reported frequencies of PGD in this category have varied considerably from as low as 10%[2] to as high as 40%.[5] In the latter study, this incidence was significantly higher than the 13% incidence observed in COPD. Patients with restrictive lung disease appear to have a risk of PGD that is intermediate to that of patients with COPD and primary pulmonary hypertension (PPH).[2,5,34,36]

Primary Pulmonary Hypertension

Several studies have suggested an association between PPH (or pulmonary arterial hypertension) and an increased incidence of PGD.[34,36] Christie et al showed an increased risk of PGD in patients with the diagnosis of PPH, independent of a variety of donor, recipient and operative factors.[2] A diagnosis of PPH was even more strongly associated with an increased risk of PGD after adjustment for recipient pulmonary artery systolic pressure (adjusted relative risk = 9.24, 95% confidence interval 1.75 to 48.8, $p = 0.009$). This implies that it is the disease state of PPH that increases the risk, rather than just the presence or severity of pulmonary hypertension.

Patients with PPH have a particular circulatory milieu. Cardiac dysfunction is universally present in PPH; differences in the chronicity and degree of right ventricular morphologic changes may explain the distinctly increased risk of PGD in PPH compared with other etiologies of pulmonary hypertension. In PPH, the hypertrophied, failing right ventricle is acutely afterload reduced at transplantation, resulting in increased shear stress on the formerly hypoxic pulmonary vascular endothelium. Shear stress leads to capillary leak and worse graft function.[37–42] In one series of patients with PPH or pulmonary arterial hypertension due to congenital heart disease, patients who underwent single-lung transplantation had a higher risk of early (<24-hour) pulmonary edema (82%) than patients who underwent bilateral lung transplantation (59%), supporting the role of shear stress.[43] In addition, patients who underwent heart–lung transplantation had an even lower risk (33%), suggesting a recipient cardiac contribution to PGD. Other small studies have not found differences between lung and heart–lung transplant recipients in terms of early post-operative non-cardiogenic pulmonary edema.[44] Alternatively, transient elevations in left ventricular end-diastolic pressure due to increased preload have been invoked to explain the high risk of PGD with apparently normal peri-operative left-sided cardiac function and euvolemia.[45] In this situation, the pulmonary edema might be misclassified as non-cardiogenic. From these observations, some have advocated beta-blockade post-operatively in patients with PPH to decrease right ventricular inotropy and shear stress and, hopefully, the risk of PGD.[46] Further study of such a potentially risky approach is necessary before recommendations can be made.

Secondary Pulmonary Hypertension

Secondary pulmonary hypertension has also been implicated as a potential risk factor for the development of PGD. Unlike PPH, however, secondary pulmonary hypertension does not consistently confer an increased risk of PGD and/or poorer short-term outcomes, according to the literature.[2,4,43,47] There are several potential confounders that contribute to the ambiguity in these earlier studies. Christie et al noted that pulmonary artery pressure had a significantly weakened association with PGD after adjustment for the diagnosis of PPH, indicating it may be the disease more than the elevated pulmonary artery pressure that is etiologic.[2] Secondary pulmonary hypertension has traditionally been all-inclusive in these studies, regardless of cause. To date, there is little information concerning the prevalence of primary graft dysfunction in patients with secondary pulmonary hypertension due to congenital heart disease. Therefore, for further discussion, it is better to focus on secondary pulmonary hypertension related to obstructive lung disease and interstitial lung disease. Huerd et al reviewed 76 consecutive single-lung transplants with pulmonary hypertension due to parenchymal lung dis-

ease.[47] They found no relation between pre-operative mean pulmonary artery pressures and PGD. In addition, they noted that both short- and long-term survival rates, as well as functional outcomes, were no different between the low and high pulmonary artery pressure groups. Dahlberg et al performed an analysis on 154 consecutive single-lung transplant recipients with advanced lung disease due to COPD.[48] Both incidence of PGD and 30-day mortality were significantly associated with elevated pulmonary artery pressure. This was true even after adjustment for the use of cardiopulmonary bypass.

Secondary Pulmonary Hypertension Due to Other Diseases

For CF patients, based on unpublished data from the ISHLT registry, there does not appear to be a significant difference in short- or long-term outcomes as stratified by normal (12 to 24 mm Hg), low (24 to 27 mm Hg) and high (27 to 49 mm Hg) mean pulmonary artery (PA) pressure by univariate analysis. There is a lack of information concerning the incidence of PGD in patients with secondary pulmonary hypertension due to congenital heart disease.

The type of transplant procedure utilized in patients with pulmonary hypertension may affect the incidence of PGD. In most of the aforementioned studies, procedure type was not accounted for in the final analysis. One recent study attempted to determine the impact of single vs bilateral transplant in secondary pulmonary hypertension patients.[49] The investigators found no survival benefit of bilateral lung transplantation in patients with secondary pulmonary hypertension, similar to the Huerd study. However, the number of patients with severe pulmonary hypertension (mean PA pressure >40 mm Hg) was quite small.

TYPE OF TRANSPLANT

Most studies of the association between transplant type and PGD are limited by univariate analyses. It is possible that an apparent association between type of transplant and the risk of PGD may be confounded by the indication for lung transplantation and the use of cardiopulmonary bypass.

Lung vs Heart–Lung Transplantation

The ISHLT registry suggests an increased early death rate due to "graft failure" for heart–lung transplant (HLT) vs lung transplant (LT) recipients[1]; however, this may be confounded by indication. That is, most LTs are performed for COPD, whereas most HLTs are performed for pulmonary arterial hypertension, making it difficult to determine whether the procedure or the underlying disease is the true risk factor. In addition, all HLTs require use of cardiopulmonary bypass. One study of 239 cases showed no difference in early deaths among single-lung transplant (SLT), bilateral lung transplant (BLT) and HLT recipients.[50]

SLT vs BLT

In the ISHLT registry, a similar peri-operative mortality was detected for SLT and BLT, regardless of underlying diagnosis.[1] Most studies investigating PGD have not identified type of transplant as a significant risk factor.[2,4,34,36] Although some studies suggest that a bilateral procedure carries a higher risk of PGD and prolonged respiratory failure, the higher prevalence of PPH and cardiopulmonary bypass use in BLT recipients likely confounds these results, as confirmed in multivariate analyses.[3,5] In addition, as the indications for SLT vs BLT vary between centers, it is difficult to interpret the bias introduced by pre-transplant factors on the association between transplant type and outcomes. One group initially reported a significantly higher incidence of PGD among COPD recipients undergoing SLT compared with BLT[51]; however, a subsequent analysis of a larger number of subjects did not reveal differences in early post-operative outcomes.[52] These investigators also found similar gas exchange at 48 hours among COPD BLT recipients utilizing cardiopulmonary bypass vs no cardiopulmonary bypass.[53] Although no effect of transplant type on short-term survival has been demonstrated in COPD,[54] older recipients (>60 years) undergoing BLT did have a significantly reduced 30-day survival of 78% vs 93% after SLT.[55] It is unknown whether this is related to a higher incidence of PGD among elderly BLT recipients.

As previously mentioned, a Washington University study found a somewhat higher prevalence of early graft dysfunction in α_1-related emphysema compared with COPD, although PGD was not specifically defined.[33] A significantly higher proportion of α_1-group patients received a BLT; however, no comparison was made between SLT and BLT. A previous study by the same group showed similar early post-transplant outcomes between transplant types, including duration of mechanical ventilation and intensive care unit stay.[54] Comparable short-term survival and duration of mechanical ventilation was observed among 13 idiopathic pulmonary fibrosis (IPF) patients receiving BLT compared with 32 after SLT, despite a much greater use of cardiopulmonary bypass (46% vs 6%) in the former group.[56] In summary, it is unlikely that type of transplant is an important determinant of PGD.

ROLE OF CARDIOPULMONARY BYPASS

The role of cardiopulmonary bypass as an independent or contributing factor for PGD remains controversial. Cardiopulmonary bypass causes a systemic, pro-inflammatory response with activation of cytokines, leukocytes and the complement cascade.[57–59] The contribu-

tion of this inflammatory response and the requirements for transfusion on early graft function are less well defined. Limited retrospective series supporting both the deleterious and non-deleterious effects of cardiopulmonary bypass have been reported.

Aeba et al studied 100 consecutive transplants and concluded that cardiopulmonary bypass worsened early graft function.[60] Patients requiring cardiopulmonary bypass had more radiographic infiltrates, larger alveolar–arterial oxygen gradients, prolonged time on mechanical ventilation, and, ultimately, decreased survival. However, the patients requiring cardiopulmonary bypass in this series also had a higher incidence of pre-operative pulmonary hypertension, potentially confounding the results. To help differentiate the effect of donor lung selection on graft dysfunction, graft function of single-lung transplants from the same donor, so called "twin recipients," was studied.[61] In this analysis, immediate graft function, but not long-term outcome, was worse in patients requiring cardiopulmonary bypass. Again, pre-operative pulmonary hypertension was more common in the group requiring cardiopulmonary bypass, potentially biasing the results. In a review of 94 patients undergoing double-lung transplantation, cardiopulmonary bypass was again associated with worse immediate graft function, more severe radiographic infiltrates, and longer intubation.[62] Cardiopulmonary bypass was found to be the strongest single predictor of prolonged intubation, and pulmonary hypertension was not found to be an independent risk factor for early graft dysfunction. Although the use of cardiopulmonary bypass was an independent risk factor, a notable difficulty in interpreting the data are the overall severity of the patient's illness or operative difficulty requiring the use of cardiopulmonary bypass.

Corroborating data from another institution can be found in a review by the St Louis–Barnes group, in a large retrospective analysis of their emphysema population.[33] In 306 lung transplant recipients without a diagnosis of pulmonary hypertension, the need for cardiopulmonary bypass at the time of operation independently predicted an increased risk of death. The study did not provide the indications for cardiopulmonary bypass and did not describe whether the heightened risk was from early graft dysfunction. Interestingly, the same group published an earlier study that did not show a significantly increased risk with the use of cardiopulmonary bypass in a cohort of non-pulmonary hypertensive patients undergoing bilateral lung transplantation.[63] However, time to extubation (4.2 ± 3.1 vs 2.8 ± 2.2 days) and time to room air (11.6 ± 10 vs 9.2 ± 10 days) appeared to be prolonged in patients undergoing cardiopulmonary bypass.

Despite worries about the effects of cardiopulmonary bypass on initial lung function in transplantation, its safe use has been well documented and accepted clinically. The University of Pennsylvania group has assessed the initial impact of cardiopulmonary bypass on lung function. Szeto et al compared 14 emphysema patients who underwent double-lung transplant with the elective use of cardiopulmonary bypass to 50 patients who underwent transplantation without cardiopulmonary bypass.[53] In their study, the use of cardiopulmonary bypass was not dictated by pulmonary hypertension or emergent intraoperative factors. The groups had a similar Pao_2:FIo_2 ratio at 1 hour, and 1 day, time of mechanical ventilation and overall hospital stay. Christie et al did not find cardiopulmonary bypass to be an independent risk factor for PGD.[2] The Stanford group reported their results with the elective use of cardiopulmonary bypass in CF patients, who generally do not require bypass for hemodynamic support.[26] Although specific parameters of early graft function were not presented, the 93% 1-year survival implied that cardiopulmonary bypass did not dramatically increase the risk of PGD. de Boer et al compared 35 emphysema patients who received cardiopulmonary bypass during transplantation (28 completely elective, 7 emergent) to 27 emphysema patients who did not.[64] No adverse effects of cardiopulmonary bypass could be found. Lung function at 1 and 24 hours was almost identical between the groups, and 1-year survival was actually better for patients who had used cardiopulmonary bypass. The survival benefit was attributed to the possible immunosuppressive effects of cardiopulmonary bypass and its subsequent effect on acute and chronic graft function.

Other theoretical benefits of the elective use of cardiopulmonary bypass have included avoiding overperfusion of the first implanted lung and resulting graft injury, and the ability to completely remove possible septic sources in CF patients before implantation and immunosuppression. Sheridan et al found no differences in function of the initially implanted lung and the second implanted lung in 23 consecutive BLT patients undergoing transplant without cardiopulmonary bypass.[65] Objective data to support the beneficial effect of removal of both septic lungs in cystic fibrosis, before implantation of the donor lungs, is not supported in the literature.

BLEEDING AND TRANSFUSION-RELATED LUNG INJURY

Transfusion of blood products may lead to pulmonary dysfunction.[66] Free radicals, cytokines and humoral factors that are produced activate neutrophils and facilitate their interaction with the pulmonary endothelium. Activated neutrophils marginate through the endothelium where they are responsible for tissue injury by the release of free radicals and proteases.[67]

In the early era of lung and heart–lung transplantation, intra-operative and post-operative bleeding were significant causes of early morbidity and mortality. Blood loss was mainly caused by problems in surgical technique, inadequate control of anti-coagulation, increased blood loss due to previous surgery, hematologic and coagulation alterations caused by cardiopulmonary bypass, and a lack of controlled reperfusion techniques. Strategies to minimize bleeding included improvements in surgical technique (clam-shell incision vs median sternotomy[68]) and the use of aprotinin[69–74]; however, these single-center reports did not focus on graft dysfunction. Subsequent studies evaluating bleeding after transplantation have also not elucidated clear links between bleeding and PGD.[27,75–78] Causes of early death or morbidity were usually separated into: (1) bleeding-related with need for transfusion or re-operation[22]; and (2) respiratory failure, prolonged mechanical ventilation or donor organ failure.[29,79] Recent analyses have shown less difficulties with excessive hemorrhage.[27,79,80]

Transfusion-related lung injury (TRALI) typically presents within 1 to 2 hours of the transfusion of a plasma-containing blood component. Patients with TRALI develop dyspnea, hypoxemia, hypotension and bilateral pulmonary edema, which is indistinguishable from acute respiratory distress syndrome (ARDS).[81] Unlike ARDS, however, the non-cardiogenic pulmonary edema of TRALI is usually transient, resolving within 72 hours. A minority of cases are fatal (6% to 10%).[82] The true incidence of TRALI is somewhere between 0.014% and 0.08% per allogeneic blood unit transfused and 0.04% to 0.16% per patient transfused,[81] but prospective studies are lacking and TRALI may be significantly underdiagnosed. The precise mechanism of TRALI is unknown and virtually every type of blood component has been implicated.[83] Unlike most immunologic transfusion reactions, the pathologic antibodies in TRALI typically are of donor, rather than recipient, origin. Class I and Class II anti-HLA and anti-granulocyte antibodies (anti-NA2, 5b, NB1, NB2) are thought to play a role and are often traced to multiparous female donors.[81] A "two-hit" hypothesis is proposed. The priming event is the underlying clinical condition (recent surgery, systemic infection, massive transfusion, hemolysis) resulting in activation of the pulmonary capillary endothelium and the priming of neutrophils that attach to the activated pulmonary endothelium.[83] The second event is the activation of neutrophils due to infusion of plasma components or lipids stored with blood components.[84]

There is one case report of TRALI developing in a single-lung transplant recipient after a transfusion of packed red cells 10 weeks after transplantation.[85] The blood donor had antibodies directed against the HLA-B44 antigen, which was present in the lung donor tissue, but not in the recipient. Not surprisingly, only the grafted lung, and not the native lung, was involved. No prospective study has focused on the roles of bleeding or TRALI in PGD. Unfortunately, the clinical presentation of TRALI may be undistinguishable from lung injury caused by other insults, making the determination of its role and incidence in PGD difficult.

SURGICAL COMPLICATIONS

Despite improvements in operative techniques, surgical problems may still lead to graft dysfunction in the early post-operative period.[86] Technical complications leading to poor graft function generally include vascular anastomotic obstruction or improper orientation of the graft. Mechanical obstruction of the left atrial cuff, pulmonary vein or pulmonary artery due to anastomotic problems and/or subsequent thrombosis is the main source of graft dysfunction after lung transplantation.

Venous Obstruction

In one prospective study, the incidence of post-transplant pulmonary venous anastomotic complications was noted to be as high as 29%.[87] Inadequate venous drainage leads to pulmonary graft edema and, if severe, can lead to hemorrhagic infarction.[88,89] Signs of obstruction appear rapidly after reperfusion and include frothy pinkish bronchial drainage, increased pulmonary arterial or venous pressures, a pulmonary infiltrate on X-ray, and hemodynamic instability, clinically mimicking reperfusion injury.[89–91] Anastomotic or thrombotic venous obstruction can be diagnosed by transesophageal echocardiogram (TEE). TEE visualizes the pulmonary veins and the left atrium and can measure the gradient across the anastomosis. Surgical correction must be performed promptly to avoid significant morbidity and possible mortality. Re-operation requires adequate protection of the graft during the ischemic period, often requiring hypothermic cardiopulmonary bypass. A thrombotic obstruction in the early post-operative period often requires surgical thrombectomy. In addition to surgical repair, thrombolytic therapy and transseptal balloon angioplasty and stenting have also proven successful in select cases.[88,89,92,93] Alternative techniques may help cope with an inadequate recipient or donor atrial cuff to provide sufficient venous drainage and avoid stenosis during the anastomosis.[94,95]

Arterial Stenosis

Pulmonary arterial stenosis can occur due to excessive length of the donor artery (more common on the right side), purse stringing of the anastomosis, or improperly placed additional sutures for hemostasis. A significant narrowing results in reduced pulmonary flow through the graft and proximal pulmonary hypertension with resultant hypoxemia presenting as worsening hypox-

emia at rest or during exercise, depending on the degree of obstruction. Hemodynamic instability may occur in severe cases.[93,96] Often a ventilation perfusion scan suggests the diagnosis, which is confirmed by a transesophageal echocardiography (TEE) or pulmonary angiogram. The left pulmonary arterial anastomosis is not always clearly visualized by TEE and, in these circumstances, a pulmonary angiogram is necessary.[95–97] Surgical revision with hypothermic cardiopulmonary bypass to protect the graft, or endovascular balloon angioplasty and stenting (which may be combined with thrombolytic therapy in the presence of thrombus), are indicated to correct the stenosis.[93,95,98–100]

Orientation of the Graft

An upside-down graft orientation usually does not cause graft dysfunction unless there is associated torsion of the bronchus or the vascular connections. Depending on the degree of torsion and resulting airway obstruction, venous drainage problems or arterial stenosis can occur. Lobar torsion in an appropriately orientated lung has been reported with severe graft dysfunction and subsequent hemorrhagic infarction.[101–103] A chest X-ray showing lobar collapse and consolidation and a bronchoscopic examination revealing obstruction of the airway supports the diagnosis. Computed tomographic images can offer further evidence for the torsion. Surgical exploration is invariably required with "detorsion" or resection of the infarcted lobe.

Reperfusion Technique and PGD

A potential cause of PGD may be directly related to the conditions and techniques involved in the initial reperfusion of the donor lung. Work over the past 30 years has characterized many of the cellular changes associated with reperfusion,[104–106] and investigators have attempted to prevent reperfusion damage by changing the content of the initial reperfusate.[34,107,108] Neutrophils play a critical role in the inflammatory cascade that follows reperfusion of an ischemic organ. Capillary plugging may lead to the "no reflow" phenomenon.[109] There may also be direct release of inflammatory cytokines as well as proteases and elastases.[110] Removal of leukocytes from the reperfusate has been shown to significantly reduce lung reperfusion injury after transplantation.[111] Experimental studies have shown that carefully controlled reperfusion with a modified reperfusate can result in improved lung function after transplantation.[39] In addition to neutrophil reduction and changes in the composition of the reperfusate, the duration of modified reperfusion and the reperfusion pressure can have a significant impact on the degree of the injury.[38,112]

Many of the aspects of reperfusate modification that have been shown to be efficacious in experimental models are now being utilized in the clinical setting by investigators at UCLA. The modified reperfusion technique utilized involves insertion of a catheter into the main or individual pulmonary artery after implantation (depending on double- vs single-lung transplantation). The recipient blood is depleted of leukocytes; supplemented with nitroglycerin; adjusted for pH and calcium level; enriched with aspartate, glutamate and dextrose; and then administered into the pulmonary arteries of the newly implanted lung(s). The modified reperfusion pressure is maintained at <20 mm Hg. After 10 minutes of modified reperfusion, the pulmonary artery clamp is removed or weaning from cardiopulmonary bypass is performed. In one small study, a group of 23 patients who underwent lung transplantation with modified reperfusion was compared to 23 matched controls.[113] No patients developed post-transplant ischemic reperfusion injury, compared with 5 patients in the unmodified control group. In addition, a trend toward improved survival was noted as well (96% vs 81%, respectively).

In a more recent report, the UCLA group expanded their study and analyzed 100 consecutive lung transplant cases in which they used this technique.[114] The initial 42 donor organs were preserved in Euro-Collins solution; the remaining organs were preserved in LPD (Perfadex) solution. Forty-two patients underwent single-lung transplantation, 5 of whom required cardiopulmonary bypass for the procedure. Fifty-eight patients underwent double-lung transplantation; all double-lung transplant procedures were performed on cardiopulmonary bypass. The mean allograft ischemia time was 310 $\pm$ 63 minutes. There were no technical complications associated with the modified reperfusion. In this cohort The mean Pao_2:FIO_2 at 6 hours was 252.3 $\pm$ 123.3. The median number of days on the ventilator was 2 (range 1 to 202 days), the median number of days in the ICU was 4 (range 2 to 202 days), and the median length of hospital stay was 14 (range 6 to 277 days). The incidence of PGD (defined as Pao_2:FIO_2 <150 with diffuse infiltrate on the X-ray in absence of other causes) in this cohort was 2.0%. The early survival (30-day or in hospital mortality) of this group of patients was 96%.

Modified reperfusion may also improve results with use of extended donors.[115,116] A recent study showed a significant increase in early mortality when non-standard criteria lungs are used secondary to an increased susceptibility to PGD because of either direct injury to the lung (i.e., pulmonary contusion), changes secondary to brain death, or volume overload.[117] The UCLA group also analyzed results in a sub-group of recipients of non–standard-criteria lungs, with respect to use of the aforementioned modified reperfusion protocol, and found that the incidence of PGD, early mortality and

1-year survival were no different than when standard donors were used.[114]

EXPERIMENTAL AND CLINICAL BIOLOGIC FACTORS AND MARKERS IN THE RECIPIENT

Lung injury begins at least at a sub-clinical level at the time of donor brain-stem death as a result of a generalized inflammatory response, which correlates with subsequent indices of oxygenation in the recipient.[118] Experimental and clinical evidence now suggests that reperfusion injury occurs in a biphasic pattern with the early phase of reperfusion injury depending primarily on donor characteristics, and the delayed phase of reperfusion occurring over the ensuing 24 hours depending primarily on recipient factors.

Upregulation of Molecules on Cell Surface Membrane

Neutrophil emigration from circulation to tissue involves the sequential events of rolling, adherence, activation and extravasation. This process occurs in PGD in both experimental and clinical scenarios. Neutrophil rolling is dependent on selectin-mediated interaction between endothelial cells (P- and E-selectin) and neutrophils (L-selectin). Adherence and activation of neutrophils occur when leukocyte β1- or β2-integrin (β chain = CD18) binds to endothelial cells expressing intracellular adhesion molecule-1 (ICAM-1) or vascular endothelial adhesion molecule-1, respectively. Neutrophil extravasation into living tissue is dependent on ICAM-1 and platelet endothelial cell adhesion molecule-1 interactions with immunoglobulins. There is clear evidence that such adhesion molecules are upregulated on the pulmonary endothelium after transplantation, and selective blockade of selectins ICAM-1 and CD18 can reduce injury.[119–124] The role of polymorphonuclear (PMN) cells in this pathway is particularly intriguing, as patients with PPH (with a high risk of PGD) have a lower threshold for the release of inflammatory products, such as elastase and superoxide.[125]

A recent study found an association between P-selectin expressing platelet aggregation in the pulmonary vasculature early after lung reperfusion and the subsequent incidence of PGD.[126] Plasma levels of P-selectin are increased in PPH, PGD and ARDS,[121,127,128] and P-selectin leads to ischemia–reperfusion injury in an animal model via PMN-cell recruitment. Blockade of P-selectin before reperfusion reduced PMN infiltration and improved graft function in this model.[121]

Prothrombotic and Fibrinolytic Factors

Tissue factor has been shown to be upregulated on endothelial cells and macrophages during hypoxia in a liver transplant model, explaining the pro-coagulant activity, which leads to the microvascular thrombosis accompanying PGD.[129] Inhibition of the classical pathway of complement by C1-esterase inhibitor has been shown to improve early lung function in both experimental and clinical lung transplantation, implicating complement activation as an important host response leading to PGD.[130,131]

Release of Pro-inflammatory Mediators—Cytokines and Chemokines, Lipids, Complement and Endothelin

Experimental and clinical studies have shown that the reperfusion of an ischemic organ induces a rapid release of pro-inflammatory cytokines and chemokines in bronchoalveolar lavage (BAL) fluid within 4 hours, including interleukin (IL)-2, tumor necrosis factor (TNF)-α and interferon-γ.[132] TNF-α, interferon-γ, IL-8, IL-10, IL-12 and IL-18 have all been measured in the lung tissue during cold ischemia and reduced levels have been reported after reperfusion, with the exception of IL-8, which is increased.[133] The age of the donor has been inversely correlated with IL-10 levels. IL-8 levels in lung tissue also negatively correlated with oxygenation, and positively correlated with the acute physiology and health evaluation score over the first 24 hours. The role of elevated IL-8 as a mediator of lung injury has been supported by experiments demonstrating reduced lung injury and neutrophil infiltration in a rabbit model of reperfusion after administration of anti–IL-8 antibody.[134] The low levels of IL-10, an anti-inflammatory cytokine, may predispose to PGD and the positive correlation with age provides a rationale for the higher incidence of PGD seen when older donors are used. IL-1 and IL-6 have also been linked to ischemia–reperfusion injury and poor outcomes after transplantation.[135,136] Interestingly, IL-1 and IL-6 may also be increased in PPH patients at baseline, possibly accounting for the increased risk of PGD in these patients.[137,138]

Phospholipase A2 has been found to increase after ischemia–reperfusion, and is capable of inducing the release of platelet activation factor (PAF), a potent mediator of inflammation, and mobilizes arachidonic acid from the membrane lipid pool. The lipo-oxygenase pathway of metabolism leads to the production of pro-inflammatory leukotrienes, which can increase capillary permeability. Phospholipase A2 comprises a growing family of enzymes differing in structure, cellular location and mechanism of release. Phospholipase A2 is increased in the BAL fluid from patients with ARDS. There is no direct evidence of phospholipase A2 activation in PGD after lung transplantation, but it has been demonstrated in other reperfusion injury models, such as in intestine.[139] The production of PAF can initiate lung injury after ischemia–reperfusion with direct evidence seen in canine lung transplant models.[140,141] Arachidonic acid metabolites, including thromboxane and leukotrienes, have been demonstrated to increase

in non-transplant lung ischemia–reperfusion injury models.[142,143]

Complement-mediated lung injury via direct and indirect mechanisms have been demonstrated after ischemia–reperfusion,[144,145] and the activated complement fragment, C5A, is also capable of amplifying injury via its chemoattractant properties. The natural complement antagonist, complement receptor 1, has been cloned into a stable form and can reduce PGD when administered to recipient pigs undergoing lung transplantation.[146,147]

Endothelin-1 accumulates in lung tissue and BAL before and during reperfusion of the transplanted lung, mediating increased vascular permeability.[148,149] Endothelin-1 levels are also increased in the plasma of patients with PPH.[150] Endothelin-1 antagonists have been found to reduce injury in experimental lung transplantation.[151]

Cell Activation—Macrophages, Lymphocytes and Neutrophils

Experimental and clinical evidence suggests that PGD occurs as a biphasic response. The early phase depends mainly on donor criteria; the second phase, occurring over the first 24 hours, depends on recipient factors. Macrophages mediate the early phase of PGD and neutrophils, and lymphocytes the subsequent phase.[152,153] The transplanted lung carries a large number of "passenger" macrophages in response to oxidative stress. These macrophages can produce inflammatory cytokines and chemokines, including TNF-α, interferon-γ, monocyte chemoattractant protein (MCP-1) and IL-8. The inhibition of pulmonary macrophages by injecting the donor with gadolinium chloride has been shown to reduce PGD in recipients.[154,155] The role of recipient-derived infiltrating lymphocytes in the genesis of PGD is not well studied. Nude mice, $CD4^+/CD8^+$ knockouts and CD4-depleted mice have significantly less reperfusion injury of the liver and kidney compared with controls.[156,157] A neutrophil-rich BAL characterizes PGD and these cells progressively infiltrate the transplanted lung over the first 24 hours after initial macrophage-induced injury. Neutrophils are not crucial to the development of injury, however, with a number of studies demonstrating PGD occurring after reperfusion in the absence of neutrophils.[158,159] Neutrophils in BAL are also a feature of bacterial infection and are not a specific marker of PGD in the first 24 hours.

Exhaled Nitric Oxide (eNO)

Many cells within the lungs produce nitric oxide (NO), which plays a critical role in the pathophysiology of the pulmonary vascular bed and airways. NO can modulate the adhesive interactions between neutrophils and endothelial cells and its production and bioactivity are subject to great alterations during hypoxia, ischemia and reperfusion. Although measurement of eNO provides important information regarding NO concentrations in the gas phase; interpretation of these data with regard to in vivo NO metabolism is difficult. The exact anatomical sites and types of cells responsible for release of NO in the gas phase remains the subject of debate,[160] although the balance of opinion now favors that changes in exhaled NO reflect altered airway epithelial NO generation and consumption. Although the potential value of eNO estimation as a marker of PGD must be viewed in that light, some investigators have employed the use of eNO after infusion of glyceryl trinitrate (GTN), a fraction of which is metabolized in the pulmonary microvasculature to NO and is diffusable into the alveolar space, increasing eNO.[161,162] No characteristic eNO patterns have emerged from studies after lung transplantation among patients undergoing cardiopulmonary bypass, although reduced GTN responses have been reported after human lung transplantation.[163] No correlation has been made with the subsequent development of PGD, and the role of this technique is yet to be fully evaluated.

SUMMARY

The lack of a clear definition of PGD in many large series of lung transplantation, including the ISHLT registry data, hampers the identification of recipient-related risk factors. Concomitant donor-related variables further confound these analyses. Based on the current body of literature, recipient-related risk factors that would require further study before any association can be stated include the type of procedure, the presence of hepatic dysfunction, and pleural adhesions and/or prior surgery, which increase the risk of postoperative bleeding. Additional factors that may confound the clinical picture or possibly contribute to the severity of the manifestations of PGD include renal impairment, left heart disease, elevated anti-HLA antibodies and secondary pulmonary hypertension.

Secondary pulmonary hypertension may increase the risk of peri-operative mortality, but this may or may not be related to an increased incidence of PGD. Studies have tended to include all etiologies of secondary pulmonary hypertension (congenital heart disease, thromboembolic disease, obstructive lung disease and interstitial lung disease), which limits the ability to determine the effect of pulmonary hypertension on PGD. In addition, most studies include data from screening right-heart catheterization at the time of listing. This limits the ability to accurately define the sub-groups of patients with and without pulmonary hypertension at the time of transplantation. Presently, there is no conclusive evidence to strongly recommend

single vs bilateral transplant for patients with secondary pulmonary hypertension.

Significant data support the safe use of cardiopulmonary bypass for lung transplantation. Possible deleterious effects on primary graft function have been documented, but do not appear to significantly impair short- and long-term outcomes. Refinements in the methods and techniques of cardiopulmonary bypass, including the use of leukocyte filters and modified ultrafiltration, will likely continue to diminish potential deleterious effects. Although there is no strong evidence to support the elective use of cardiopulmonary bypass in the absence of hemodynamic or intra-operative factors, its use should not be deferred secondary to fear of graft dysfunction. Beyond the issue of PGD, other concerns, such as bleeding with increased need of blood and/or blood products as well as overall resource utilization, may support the role of primary lung transplant without cardiopulmonary bypass.

Presently, the strongest and most clearly established recipient risk factor for primary graft dysfunction is the diagnosis of PPH. Further research into the mechanism of PPH-associated PGD could well lead to advances in preventing or treating this syndrome in all patients after lung transplantation. The other strong recipient-related factor appears to be the technique utilized for lung reperfusion. Based on the early series of clinical experience utilizing modified reperfusion, this extremely promising method may greatly decrease the incidence of PGD. It may also allow the use of non-standard donor criteria lungs in a safer fashion. Finally, all studies of recipient-related risk factors for PGD need to be analyzed in the context of concomitant donor-related risk factors.

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