Report of the ISHLT Working Group on Primary Lung Graft Dysfunction Part VI: Treatment

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1. GENERAL PRINCIPLES OF POST-OPERATIVE MANAGEMENT OF LUNG TRANSPLANT PATIENTS WITH PRIMARY GRAFT DYSFUNCTION

The general principles regarding immediate post-operative care in patients undergoing lung transplantation have been outlined in several review articles.[1–3] Patients with post-transplant primary graft dysfunction (PGD) are, by and large, treated like patients with acute respiratory distress syndrome (ARDS), given some similarities between the two entities (i.e., severe hypoxemia and radiographic evidence of diffuse alveolar infiltrates). Yet, there have been no clinical studies that have systematically and specifically evaluated the effect of various modalities (such as mechanical ventilation, fluid management, circulatory support, etc.) on the development of PGD and/or the outcome of patients with PGD. As a result, no firm consensus currently exists regarding the optimal post-operative care strategy.

In general terms, the overall treatment goals should be to avoid excessive fluid administration in the setting of a leaky capillary syndrome, while providing adequate perfusion of vital organs and the bronchial anastomoses.[2] This may usually be achieved by combination of relative fluid restriction and low-dose systemic vasopressors, with or without pulmonary vasodilators. The inevitable various degrees of renal dysfunction (secondary to azotemia and acute tubular necrosis) should be tolerated, with a low threshold for temporary ultrafiltration or dialysis support.

2. FLUID MANAGEMENT

Correction of fluid losses should be done cautiously, while optimizing hemoglobin and the coagulation status. There are no specific studies to support this, but general practice is to keep the hematocrit in the range of 25% to 30%. Coagulopathy is corrected with the administration of fresh-frozen plasma or specific coagulation factor replacement as required.

3. VENTILATORY MANAGEMENT OF PATIENTS WITH PGD

As mentioned earlier, no studies are currently available evaluating different ventilatory modes in patients with PGD. PGD and ARDS share a number of similar clinical, radiographic and histologic features.[4] The currently accepted definitions of acute lung injury (ALI) and ARDS, as defined by the American–European Consensus Conference in 1994, are: acute onset of poor oxygenation (ratio of arterial oxygen to the fraction of inspired oxygen, or P/F ratio of $\leq$300 for ALI and $\leq$200 for ARDS); bilateral pulmonary infiltrates on chest X-ray; and lack of left atrial hypertension.[5] In comparison, the current recommendation for definition of PGD, as suggested by the ISHLT Working Group on Primary Graft Dysfunction (outlined in Part II of this series "Definition of PGD," by Christie et al), are the presence of radiographic infiltrates consistent with pulmonary edema, and various degrees of hypoxemia. Therefore, it seems reasonable to extrapolate what we have learned from the ARDS experience to the management of PGD and to carefully adapt the current recommendations for ventilation in ARDS to patients with PGD.

Traditionally, the approach to mechanical ventilation in ARDS was to apply tidal volumes of 10 to 15 ml/kg body weight, to maintain normal Pa_{O_2} and Pa_{CO_2} levels.[6] In patients with injured lungs, this often leads to high peak inflation and plateau pressures, with risk of over-distension of the lungs and a significant risk of volutrauma and barotrauma.[7] Moreover, a significant amount of experimental data in animals suggests that over-distension of the alveoli perpetuates lung injury with induction of cytokine release, leading to further lung injury or biotrauma[8,9] and dysfunction of other distant organs. As a result, an approach of "protective ventilation" has been developed.[10,11] This approach combines smaller tidal volumes (6 to 8 ml per kilogram of body weight), which limit alveolar distension while

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maintaining opening of small airways with elevated positive end-expiratory pressure (PEEP), lower plateau pressures (≤30 cm H_2O) and higher-frequency ventilation with volume assist-control ventilatory mode. The ARDS Network Study, a multicenter randomized trial, compared a traditional ventilation strategy with the "protective" approach in patients with ARDS. The study was stopped prematurely after an interim analysis showed significantly lower mortality in the group ventilated with the protective approach.[10] Based largely on this study, as well as on smaller previously reported studies, the "protective ventilation" approach, using pressure-controlled ventilation mode,[7] is now widely accepted as the recommended ventilation mode for patients with ARDS.

Additional adjunct approaches to the respiratory management of ARDS, such as the use of prone positioning,[12,13] permissive hypercapnia, inverse ratio ventilation and high-frequency ventilation have been evaluated, and may be applied in some patients.[7]

With specific reference to pulmonary PGD, the only study to date examining ventilation-induced lung injury in lung transplantation was an animal study performed by the University of Toronto group.[14] In a rat lung transplant model, traditional ventilation was compared with a "minimal mechanical stress" mode (significantly lower tidal volumes, with adjusted higher PEEP). Animals ventilated with the "minimal stress" mode showed significantly higher oxygenation, as well as lower cytokines release and fewer morphologic signs of injury. In this setting, it is considered that the injurious ventilation provides the "second hit" in a two-hit injury model, the first hit being lung transplantation injury.

Emphysema patients with PGD after single-lung transplant may require independent lung ventilation (ILV) because of the significantly different mechanical properties of the transplanted lung and the native emphysematous lung. In this setting, conventional mechanical ventilation with high PEEP levels and high tidal volumes, in an attempt to improve the dysfunctional allograft, may result in hyperinflation of the native emphysematous lung. This has been shown to cause over-distension of the alveoli in the native, more compliant lung. As a result, the pulmonary vascular resistance in the native lung is elevated, with significant shunting of blood to the allograft. This, together with mediastinal shifting away from the hyperinflated native lung (resulting in impaired cardiac venous return) may significantly compromise the patient. Double-lumen endotracheal intubation and two synchronous ventilators with different ventilation modes to each lung have been employed successfully in a few reported cases.[15–17]

In summary, there are currently no clinical studies to suggest superiority of one ventilatory mode over the other. Yet, based on the available data for treatment of ARDS, we suggest that patients with PGD after lung transplantation should be ventilated using a protective mechanical ventilation approach. Further randomized, controlled studies are needed to determine the optimal mode of ventilation in the specific setting of post-transplant lung dysfunction.

4. NITRIC OXIDE

Nitric oxide (NO) plays a critical role in maintaining the homeostasis of pulmonary circulation. NO induces intracellular cGMP production, which in turn provides pulmonary vasodilation, maintenance of pulmonary capillary integrity, and prevention of leukocyte adhesion and platelet aggregation.

In lung transplantation, retrieval of donor lungs and reperfusion are associated with a marked decline in endogenous NO and cGMP levels.[18] The under-production of NO by the transplanted lung leads to several pathologic processes: (1) Increased pulmonary vascular resistance—several studies have demonstrated that the administration of NO or NO donors to the transplanted lung results in a decline in pulmonary vascular resistance.[19–21] (2) Increased leukocyte adhesion to the endothelial cells, leukocyte sequestration, platelet aggregation and oxidant injury. NO is known to inhibit neutrophil adhesion to endothelial cells. Administration of NO has been shown to inhibit neutrophil and platelet sequestration into the lung allograft.[22,23] (3) Increased endothelin-1 (ET-1) production—ET-1 is a potent vasoconstrictor peptide, with mitogenic as well as apoptotic effects on vessel wall cells.[24] NO is known to inhibit the synthesis of ET-1.[25] Administration of NO to the transplanted lung theoretically should prevent or attenuate these pathologic processes.

Despite encouraging results from experimental studies,[26,27] prophylactic administration of inhaled NO in clinical studies does not appear to prevent PGD. In a prospective, randomized, blinded, placebo-controlled trial of 84 patients, Meade et al demonstrated that administration of NO starting at 10 minutes after reperfusion did not affect the incidence of PGD (NO group, 22%; control group, 19%; p = NS).[28] Another study also showed that administration of NO at reperfusion does not prevent or reduce the incidence of PGD when compared with historic cohorts.[29] In a cohort of 14 patients, early administration of NO (on arrival to ICU) was associated with an incidence of PGD similar to the historic control group (NO group, 28%; control group, 32%; p = NS).[30]

Inhaled NO has been useful clinically to treat PGD in lung transplantation (based on its ability to reduce pulmonary artery pressures without affecting systemic pressures, combined with improvement in ventilation perfusion matching). However, there are no prospec-

tive, randomized clinical studies comparing NO to placebo in treatment of established PGD after lung transplantation. Several reports of case series have suggested that administration of NO is associated with improved clinical outcome.[31–33] However, there have been other reports suggesting that administration of NO in the setting of PGD does not affect clinical outcome (number of subjects: 9 treated with NO vs 8 treated with nitrogen).[34]

In comparison to ARDS, in reviewing the current evidence for NO treatment in patients with established acute lung injury (ALI/ARDS), the results seem to reflect the same tendency. In a multicenter, randomized, controlled trial, 385 patients with moderately severe ARDS were randomized to placebo or inhaled nitric oxide at 5 ppm. NO administration improved oxygenation transiently, but the mortality and time of assisted ventilation were similar between the groups.[35] A recent systematic review that included five randomized, controlled trials on inhaled NO for acute hypoxemic respiratory failure (in adults and children) concluded that improved oxygenation was seen up to 72 hours from initiation of treatment, but there was no evidence of effect on the duration of mechanical ventilation or on mortality.[36]

With regard to dosage, most of the clinical studies examining prophylaxis against PGD or as therapy for established PGD have used a NO concentration of 20 ppm. Experimental studies have used a range of NO concentrations.[34,37,38] It is not known what dose of NO prevents PGD (if any). In reference to its therapeutic effects in established PGD, the beneficial effect of NO appears to be in the range of 10 to 20 ppm.

Side effects of NO administration include methemoglobinemia (<2% incidence in most clinical studies using 20 ppm), rebound pulmonary hypertension (especially during the weaning process—usually only in patients that have been on NO for a prolonged period of time),[39] and potential enhanced oxidant injury due to production of nitrogen dioxide and peroxynitrite during the early reperfusion period.[34,40]

In summary, inhaled NO therapy appears to be useful for improving gas exchange in cases of established PGD, but there are currently no randomized studies to support its use for ventilatory or survival benefit. It is generally used clinically where hypoxemia and/or elevated pulmonary arterial pressure (PAP) is a problem. However, the rationale for its use as a prophylaxis in preventing PGD is unproven. Its beneficial effect in treating established PGD is probably transient, as shown in the ARDS studies, but it may provide the treating team with an opportunity to stabilize the patient and optimize other factors, possibly with better outcome.

At the moment, we cannot recommend routine prophylactic use of NO. In cases of established severe PGD, we believe that it is justified to use NO selectively for patients with severe hypoxemia and/or elevated PAP, as part of the overall treatment modalities. The beneficial effect of NO, although transient, will help to maintain the patient's stability and might prevent the need for extracorporeal membrane oxygenation (ECMO) or retransplantation.

5. PROSTAGLANDINS

There is increasing evidence that prostaglandins mediate pathophysiologic functions such as inflammation and regulation of blood flow and thus may play an important role in ischemia–reperfusion injury. Prostaglandin production is initiated by the release of the fatty acid arachidonic acid (AA) and dihomogammalinolenic acid (DHLA) from membrane phospholipids. AA is a precursor for numerous prostanoids including the two-series prostaglandins (e.g., prostaglandin E_2, PGE_2), whereas DHLA is the precursor for the one-series prostaglandins (e.g., prostaglandin E_1, PGE_1).

PGE_1 has been utilized by many centers as an additive to intracellular preservation solutions based on experiments in animal models of lung transplantation demonstrating better graft function with PGE_1. Investigators hypothesized that the vasodilatory properties of PGE_1 permitted a more rapid and effective distribution of preservation fluid.[41,42] More recent studies have shown that the beneficial effects of PGE_1 occur through multiple mechanisms, and are mediated by an increased production of cyclic-3′,5′ adenosine monophosphate (cAMP), which reduces neutrophil adhesion, capillary permeability and platelet aggregation in addition to vasodilation.[43,44]

Many centers also administer PGE_1 intravenously to lung transplant recipients to reduce the severity of ischemia–reperfusion injury. This practice is based on observations of a canine lung transplant model where intravenous PGE_1 led to improvements in arterial oxygen tension and alveolar–arterial oxygen pressure difference.[45] Although the beneficial effects were attributed to vasodilation and subsequent reduction in sheer stress injury to the graft endothelium, the fact that other vasodilators did not lead to similar effects suggests that intravenous PGE_1 has other protective properties.[46,47] Recently, several investigations have started to unveil the mechanisms of these protective properties. In vitro studies have shown that PGE_1 can inhibit apoptosis by upregulating the Bcl-2 protooncogene. In addition, PGE_1 downregulates pro-inflammatory cytokines and upregulates anti-inflammatory cytokines. In a rat single-lung transplant model, PGE_1 shifts the cytokine response from a Th1- to a Th2-cytokine profile.[48] Models of liver and lung transplantation have shown that platelet aggregation in graft capillaries may contribute to ischemia–reperfusion injury.[49] Thus, the ability of

PGE_1 to inhibit platelet aggregation may have beneficial effects.[50] In fact, a prostaglandin I_2 analog that possesses potent anti-platelet activity was recently shown to reduce platelet accumulation and ischemia–reperfusion injury in a rat lung transplant model.[51]

Aerosolized PGE_1 has been utilized as an adjunct treatment in an attempt to improve ventilation/perfusion mismatching and oxygenation in patients with different types of acute lung injury, including PGD after lung transplantation.[52] In a rabbit model of warm ischemia–reperfusion injury, administration of aerosolized PGE_1, PGI_2 or nitroprusside at the onset of ischemia resulted in a dramatic reduction in lung injury.[53] Low-dose PGI_2 administration in conjunction with Rolipram, a cAMP-specific phosphodiesterase inhibitor, also resulted in similar benefits, once again highlighting the central role of cAMP in attenuating lung injury. The requirement for administration before onset of ischemia suggests a possible role in donor management with these agents.[54]

In summary, in the treatment of severe PGD, a low-dose PGE_1 infusion appears to be helpful, and is supported by evidence in animal studies. However, currently, there are no available data from humans studies to support this approach, as PGE_1 has not been tested as an isolated treatment method in a randomized clinical study setting. Further clinical trials are required to examine the role, both prophylactic and therapeutic, of prostaglandins in the management of PGD after lung transplantation.

6. SURFACTANT

Pulmonary surfactant is composed of 90% lipids, mainly phosphatidylcholine, and approximately 10% proteins, including the surfactant apoproteins A–D.[55] It is synthesized by Type II pneumocytes where it is stored in secretory vesicles as lamellar bodies.[56] The saturated form of phosphatidylcholine- dipalmitoyl phosphatidylcholine has the unique capacity to reduce the surface tension of the alveoli. By forming a stable monolayer, it stabilizes the alveoli during end-expiration, prevents atelectasis and alveolar edema, and allows an optimal surface area for gas exchange.[57] Bronchoalveolar lavage (BAL) studies usually refer to 2 sub-types of intra-alveolar surfactant: (1) large aggregates or heavy forms, largely corresponding to tubular myelin—which are highly active in decreasing the alveolar surface tension; and (2) small aggregates or light forms, largely corresponding to degraded and inactive small unilamellar vesicles.[58]

Ischemia–reperfusion injury related to lung transplantation leads to changes in the surfactant composition and function.[59–61] Clinical and experimental studies have found that ischemia, cold storage and especially reperfusion lead to an increase in the small to large surfactant aggregate ratio, an increase in sphingomyelin, and a decrease in phosphatidylglycerol and phosphatidylcholine, which correlate with decreased pulmonary compliance. In the clinical setting, this promotes alveolar collapse, ventilation–perfusion mismatch and pulmonary edema with decreased oxygenation.[59,62,63]

Experimental studies have shown that exogenous administration of surfactant can protect against the harmful effects of storage and reperfusion. In studies with mini-pigs and dogs in which donor animals exposed to various methods of ventilation and ischemia-induced damage were either treated with surfactant or served as control, treated animals showed superior oxygenation and lung compliance compared with untreated animals.[64–67] Analysis of BAL fluid in treated animals showed higher amounts of total surfactant phospholipids, a higher percentage of large aggregates and larger amounts of surfactant protein A (SP-A), which has been shown to improve the oxygenation and compliance of the transplanted lung.[66,68,69] Early pre-retrieval surfactant administration to the donor lungs led to results superior to those of animals treated only during reperfusion. The early administration likely leads to a better distribution of the preservation solution.[70–73] Administration of SP-A–enriched surfactant showed better results compared to treatment with SP-A–deficient surfactant.[64,68] As compared with endogenous surfactant, exogenous surfactant seems to be converted into its inactive form at a slower rate.[65] Use of repeated administrations (both in donor and recipient) with the combination of aerosolized application appears to achieve superior results.[71,72]

The clinical use of exogenous surfactant in human lung transplantation has been reported upon by the Hannover group. Strüber and co-workers reported the successful treatment of a patient with severe reperfusion injury who was administered nebulized surfactant.[74] The same group later reported their experience with 6 patients with PGD treated in the same manner. PGD was defined up to 6 hours after the transplantation. Immediate instillation of continuously nebulized surfactant led to improvement in the oxygenation and compliance of the allografts, and faster extubation. Time to extubation and time in the intensive care unit were not significantly different when compared with a group of 24 patients operated upon during the same time-frame and who did not develop PGD.[75,76] The same investigators recently reported on preliminary results of a randomized trial, where 100 mg/kg bovine surfactant was given as a donor pre-treatment 30 minutes before organ retrieval. Early results showed better lung function in the treated group as compared with the control group.[77]

In conclusion, the experimental findings and early clinical experience indicate that exogenous surfactant therapy is a promising therapeutic intervention for patients with PGD. Prospective, randomized studies are needed to confirm these results. These future studies will need to address issues such as the role of prophylaxis vs treatment, the type of surfactant to be given, doses, routes of administration and timing and duration of therapy.

7. NOVEL TREATMENT STRATEGIES

(a) Complement Inhibition

After promising experimental studies using the complement inhibitor, soluble complement receptor-1 (sCR1),[78,79] as well as few reported cases of successful application of complement inhibition in patients with PGD,[80] a multicenter, randomized, double-blinded, placebo-controlled trial was conducted in 59 lung transplant recipients.[81,82] Among 28 patients receiving a dose of sCR1 before reperfusion, 14 (50%) were extubated within 24 hours—significantly better than the control arm in which only 6 of 31 (19%) patients were extubated during this time-frame. In addition, the overall duration of mechanical ventilation and length of ICU stay tended to be shorter in the group receiving the therapeutic drug. The effect of sCR1 appeared to be stronger in the group of patients who underwent cardiopulmonary bypass, although the results did not reach statistical significance because of the small number (n = 12) of patients. This likely reflects the added potential benefit of inhibiting complement activation related to cardiopulmonary bypass. No sCR1-related adverse effects were reported.

(b) Platelet-activating Factor Antagonist

Wittwer and colleagues reported their clinical experience with an antagonist of platelet-activating factor (PAF; BN 52021) in 24 patients randomly assigned to either a high dose of antagonist in the flush solution and after reperfusion (n = 8), a low dose of antagonist in the flush solution and after reperfusion (n = 8), and a control group (n = 8).[83] They observed a significant improvement in the alveolar–arterial oxygen difference during the first 12 hours after reperfusion and better chest X-ray score in the two groups receiving the antagonist, as compared with the control group. After 32 hours, however, the difference was less striking, and did not reach statistical significance. In clinical kidney transplantation, a randomized, double-blinded, single-center trial with 29 recipients showed a significant reduction in the incidence of primary graft failure after transplantation in the group of patients receiving the PAF antagonist.[84]

(c) Other Agents to Prevent or Treat PGD

Numerous agents and novel strategies have been used, primarily in animal models, to prevent or treat PGD after lung transplantation. Examples of such studies include those involving the administration of free-radical scavengers or angiotensin-converting enzyme (ACE) inhibitors such as captopril,[85] anti-thrombin III as an anti-inflammatory agent[86] or matrix metalloproteinase (MMP) inhibitors[87]—with varying degrees of efficacy for attenuation of PGD. Finally, the University of Lund group proposed induced hypothermia as a treatment method for patients with pulmonary PGD. Initially reported as case report of 2 patients with severe PGD treated by induced hypothermia of 32° to 35°C with subsequent recovery,[88] they further tested this method in an animal model. In their study, induced hypothermia caused a significant reduction in right ventricular workload, although the pulmonary vascular resistance increased.[89] All published clinical reports in this context are either case reports or case series. As such, their impact on the treatment of PGD is, at the moment, questionable.

In summary, only three randomized, double-blind, placebo-controlled trials evaluating the prevention and treatment of PGD during lung transplantation have been reported. The NO prophylaxis study (Meade and colleagues) showed no demonstrable difference in clinical outcomes, whereas the complement-inhibition[81,82] and PAF-antagonist[83] small-sample studies showed favorable early clinical parameters, but did not report on long-term outcomes.

PGD is clearly the result of a multifactorial injury process. As we learn more about the specific mechanisms responsible for the different components of this complex injury, additional specific target therapies will be developed. Multicenter trials will be needed to evaluate the potential clinical impact of these novel treatment strategies as they are developed.

8. TREATMENT OF SEVERE PGD

(a) Extracorporeal Membrane Oxygenation

Most lung transplant programs reserve ECMO as a back-up in the event of severe, life-threatening PGD. ECMO has been used to treat neonatal respiratory failure, with excellent results.[90] Survival after ECMO treatment for adults with respiratory failure was less favorable, but recent series have demonstrated better outcomes, with survival of up to 55%.[91] In the adult lung transplant population, ECMO may serve as a life-saving measure for patients with severe forms of PGD who do not respond to maximal conventional treatment. In this setting, ECMO may be the only way to provide the patient with adequate oxygenation and gas exchange while avoiding the additional detrimental

effects of aggressive ventilation and persistent hypoxemia.[92–94] When severe PGD is combined with hemodynamic instability and cardiac compromise, ECMO treatment enables adequate systemic perfusion and cardiac support as well.[92,95,96]

There are two possible modes of applying ECMO support. The veno-venous (VV) mode provides only pulmonary support, and is therefore indicated in hemodynamically stable PGD patients with adequate cardiac function, whereas the veno-arterial (VA) mode is indicated in patients with a combination of graft failure and inadequate cardiac performance.

With regard to cannulation site, several groups have advocated direct cannulation of the ascending aorta and right atrium. This approach has the potential benefits of lower rate of vascular complications, especially in small patients and in women with small femoral vessels,[92] as well as of avoiding the possible detrimental effects of retrograde flow through the femoral arterial cannula, which may provide inadequate coronary arterial perfusion[97] or may create a situation in which the lower half of the body receives well-oxygenated ECMO blood while the upper body receives poorly oxygenated blood from the lungs through the ejecting heart.[98] The major disadvantages of this method are the need for re-exploration of the chest for cannulation and decannulation, with potentially more infectious complications. Other groups have routinely used the femoral vessels as the cannulation site.[99]

Originally published as case reports,[95,100,101] ECMO use for PGD has subsequently been reported in larger series.[92,94,102,103] Clearly, the results have improved over the past two decades with increasing experience and particularly with refinements in the indications.

The St. Louis group retrospectively reviewed their experience with 12 patients (2.7% of 444 lung transplant recipients). Eleven of 12 were females, 5 of whom had pulmonary hypertension (PHT). Most (10 of 12) were bilateral lungs transplants (BLTs). Seven patients (58.4%) survived, including 1 of 2 patients who underwent re-transplantation while being supported by ECMO. All survivors had ECMO instituted either perioperatively or during the first post-operative day.[92]

The Pittsburgh group reviewed 8 (3.6%, 5 BLTs) patients who required ECMO support after lung transplant.[102] All patients had their ECMO started within 10 hours post-transplant (5.6 ± 3.2 hours, range 0 to 10). Seven patients were successfully weaned and 6 (75%) were discharged home. The same group reported their results in a larger number of patients (n = 16) and compared patients with "early" (up to 7 days post-transplant) ECMO institution (10 patients, 7 long-term survivors) to those with "late" (>7 days) ECMO placement (6 patients, no survivors).[94]

In the Minnesota group experience, 14 patients (5.5%) received post-transplant ECMO support. Nine patients had early (≤24 hours) graft failure, and 7 of them were successfully weaned. Five patients had late (>7 days) graft failure and none of them could be weaned off ECMO, resulting in a mortality of 100%.[103]

In reviewing the published reports, it is evident that the morbidity related to the initiation and maintenance of the ECMO circuit is substantial, including re-exploration for bleeding or cardiac tamponade (25% to 80%), renal failure requiring dialysis (up to 70%), sepsis (up to 78%), massive stroke (embolic or hemorrhagic) and vascular complications requiring interventions. The striking relationship between the early institution of ECMO and better outcomes, as well as the fact the ECMO is most often applied on an emergent basis in a rapidly deteriorating patient, led clinicians to attempt and determine parameters that would allow prediction or early recognition of severe PGD requiring major support. Originally used for patients with acute lung injury,[104] the "oxygenation index" (OI) [OI = mean airway pressure × Fio_2/Pao_2) has been advocated by the University of Virginia group as a predictor for the need for ECMO post-transplant. In their experience, an increase in the index to ≥30 was an early predictor for severe PGD requiring major intervention (mostly ECMO), with better survival for patients who were placed on ECMO as soon as the index elevation was recognized.[93] Currently, there are no additional reports evaluating this parameter as an indication for early ECMO institution in PGD.

Although it is difficult to prove, it may well be that patients who are at higher risk for developing post-transplant PGD might theoretically benefit from prophylactic use of ECMO, instituted at the initiation of the transplant. This concept has not been systematically evaluated, but several groups have adapted the use of ECMO instead of cardiopulmonary bypass (CPB) in various patient populations.[99,105,106]

The Vienna group reported their results with 17 consecutive PHT patients who were routinely put on VA ECMO after induction of anesthesia, continuing it throughout the transplant. The ECMO was discontinued immediately after surgery (3 patients) or up to 12 hours after the surgery. There was 1 post-operative death, and 0 of 17 patients developed PGD. The group from the National Taiwan University in Taipei reported their results with the same strategy. They used ECMO instead of CPB in 5 patients with PHT. All patients could be weaned shortly after completion of the transplant and showed excellent graft function.[105] Both groups recommended the prophylactic use of ECMO as a replacement for CPB in high-risk patients, advocating the theoretical benefits of optimally controlled reperfusion

of the newly implanted graft as well as of avoidance of the detrimental effects of aggressive ventilation.

A review of previous studies evaluating clinical risk factors for PGD post-transplant shows that, in most reports, recipient diagnosis of PHT was identified as an independent risk factor. In a cohort study of 255 consecutive lung transplants, Christie et al identified PHT as one of the risk factors for development of PGD (adjusted odds ratio 4.52, $p = 0.018$).[4] Other reports have supported this observation. We therefore believe that patients with PHT undergoing lung transplantation should be closely monitored for early recognition of PGD, with low threshold toward early installation of ECMO. At the moment, we cannot recommend *prophylactic* institution of ECMO for patients with PHT, but a prospective, randomized, controlled study is clearly appropriate to further evaluate this issue.

With regard to long-term outcomes, the Minnesota group has recently reviewed their results in this patient population. For 16 ECMO patients, the 90-day and 2-year survival rates were 63% and 50%, respectively. Neither severe PGD nor ECMO use was considered a risk factor for developing bronchiolitis obliterans syndrome.[107]

In summary, ECMO is a potentially life-saving treatment option for patients with severe PGD after lung transplantation, who are not improving with conventional supportive therapy. Each individual patient should be carefully considered with regard to other co-morbidities to determine the overall likelihood of salvagability. Currently, available data indicate that *early* (<24-hour) institution offers a significant survival benefit—an important lesson learned from the early experience when ECMO was used too late as a last resort measure in terminally decompensated patients. Further studies are needed to determine the specific parameters that can enable earlier recognition of patients who will probably require ECMO. We suggest that ECMO should not be initiated later than 7 days post-transplant, as there were virtually no survivors within this group of patients. Unless used as a bridge to re-transplant, the duration of ECMO in this setting should not be prolonged, given the substantial complications related to the continuous use of the circuit, as well as the fact that most of the patients that cannot be weaned off ECMO after 4 to 7 days will not survive, as shown in the published experience. Select patients, who may be at a higher risk for developing PGD post-transplant, may benefit from prophylactic institution of ECMO at the beginning of the surgery, with continuous ECMO-assisted respiratory and hemodynamic support during surgery, enabling optimally controlled ventilation and graft reperfusion methods as well as controlled early post-transplant management.

(b) Re-transplantation

Pulmonary re-transplantation now accounts for about 2% of all lung transplant operations.[108] Yet, the literature regarding lung re-transplantation as a treatment method for PGD is limited.[109–117]

Original reports regarding pulmonary re-transplantation derived from single-center experiences.[90,105–107] Wekerle and colleagues reported the University of Vienna experience with 20 pulmonary re-transplantations performed between 1986 and 1995. Of these, 7 were re-transplanted with the diagnosis of primary graft failure. All 7 patients were on ventilatory support at the time of re-transplantation. Two survived 5 and 22 months after the re-transplant. Thus, the 1-year survival for patients re-transplanted for PGD was 22%.[105] In several additional reports, the number of patients re-transplanted for PGD varied between 3 and 5, with only occasional survivors.[94,110,111]

A comprehensive analysis of the international experience was performed by Novick and colleagues, who initiated the International Pulmonary Re-transplant Registry in 1991.[112–117] The latest updated report was published in 1998 and included 230 patients re-transplanted in 47 centers between 1991 and 1997. Fifty-two patients from this group were re-transplanted for PGD (with median interval of 15 days between transplants). Univariate analysis revealed the following risk factors to be associated with survival: (1) obliterans bronchiolitis (OB) vs non-OB as the indication for re-transplantation; (2) ambulatory status before re-transplantation; (3) ventilator support; (4) the interval between transplants (>2 or ≤2 years); (5) donor cytomegalovirus status; and (6) donor–recipient ABO blood group identity. Although there was a 22.6% prevalence rate for patients requiring re-transplantation for PGD, multivariate analysis did not find PGD to be a significant risk factor for morbidity and mortality. The only significant multivariate risk factors for worse outcome were non-ambulation and ventilator dependence, followed by earlier (before 1991) date of the re-transplant—reflecting center experience in re-transplantation.[113]

The overall Kaplan–Meier survival for the entire 230-patient cohort was 47 ± 3% at 1 year and 33 ± 4% at 3 years. For comparison, the most recent published analysis from the ISHLT/UNOS database, evaluating survival rates for the entire ISHLT registry between April 1998 and March 2002, revealed survival rates of 57.3% and 41.6% at 1 and 3 years, respectively, for pulmonary re-transplantation (ISHLT website, 3.2004). The group of patients undergoing re-operation for PGD was not analyzed separately in the registry report, and data specifically related to this group (donor and recipient characteristics, ECMO use as bridge to re-transplant, prevalence of

multiorgan failure, etc.) were not provided. Therefore, survival for this specific group is not defined. It should be noted that the combination of (1) very short interval between the two transplants for patients with PGD and (2) ventilator dependence (which by itself leads to a 40% 6-month actuarial survival in this report) resulted in notably inferior survival rates. The investigators concluded that non-ambulatory, ventilated patients should not be considered for re-transplantation with the same priority as other candidates.[113] A separate analysis from the registry report indicated that, in the setting of severe multiorgan failure, the peri-operative mortality in pulmonary re-transplantation exceeds 90%.[117]

Additional surgical considerations that are highly relevant in the setting of consideration for acute re-transplantation for PGD are: (1) what kind of re-transplant should be performed? (single vs bilateral)—with or without relation to the original surgery; and (2) in cases of PGD in patients after single-lung transplant, should the transplanted lung be removed if a single re-transplant is planned? These issues have been discussed occasionally at meetings, but to date no analyzed data are available.

To summarize, re-transplantation may be considered in highly selected patients with pulmonary PGD. Optimal donor organs should be used for patients without other end-organ failure. It is clear that this sub-group of patients represents a very high-risk population with a poor predicted survival.

In conclusion, the process of lung transplantation is associated with multiple types of injuries that ultimately manifest in a syndrome that we refer to as primary graft dysfunction (PGD). All patients, by definition, have some degree of PGD. Thankfully, in most it is relatively mild to moderate and can be managed with standard supportive therapy in the intensive care unit. In some patients, however, PGD can be severe. Management of these patients can be challenging and requires advanced supportive and therapeutic measures. The goal is to support the patient while the injured lung recovers, to treat the lung, and to avoid adding further injury to the already injured lung.

The ultimate manifestation of PGD is the summation of injury related to the donor lung, the transplant process (retrieval, preservation, implantation and reperfusion) and recipient factors. As we learn more about the mechanisms of injury underlying each of these phases of transplantation, we will be able to develop strategies to specifically ameliorate each component of the injury seen, and hopefully to ultimately improve the safety and long-term outcomes after lung transplantation.

REFERENCES

1. Snell G, Klepetko W. Perioperative lung transplant management. Eur Respir Mon 2003;26:130–42.
2. Chakinala MM, Kollef MH, Trulock EP. Critical care aspects of lung transplant patients. J Intensive Care Med 2002;17:8–33.
3. Goudarzi BM, Bonvino S. Critical care issues in lung and heart transplantation. Crit Care Clin 2003;19:209–31.
4. Christie JD, Kotloff RM, Pochettino A, et al. Clinical risk factors for primary graft failure following lung transplantation. Chest 2003;124:1232–41.
5. Bernard GR, Reines HD, Brigham KL, et al. The American European consensus conference on ARDS: definitions, mechanism, relevant outcomes and clinical trials coordination. Am J Respir Crit Care Med 1994;149:818–24.
6. Marili JJ. Evolving concepts in the ventilatory management of acute respiratory distress syndrome. Clin Chest Med 1996;17:555–75.
7. Malarkkan N, Snook NJ, Lumb AB. New aspects of ventilation in acute lung injury. Anaesthesia 2003;58: 647–67.
8. Imai Y, Parodo J, Kajikawa O, et al. Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. JAMA 2003;289:2104–12.
9. Slutsky AS. Basic science in ventilator-induced lung injury: implications for the bedside. Am J Respir Crit Care Med 2001;163:599–600.
10. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301–8.
11. Kopp R, Kuhlen R, Max M, Rossaint R. Evidence-based medicine in the therapy of the acute respiratory distress syndrome. Intensive Care Med 2002;28:244–55.
12. Pelosi P, Tubiolo D, Mascheroni D, et al. Effects of the prone position on respiratory mechanism and gas exchange during acute lung injury. Am J Respir Crit Care Med 1998;157:387–93.
13. Gattinoni L, Tognoni G, Pesenti A, et al. Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med 2001;345:568–73.
14. de Perrot M, Imai Y, Volgyesi GA, et al. Effect of ventilator-induced lung injury on the development of reperfusion injury in a rat lung transplant model. J Thorac Cardiovasc Surg 2002;124:1137–44.
15. Gavazzeni V, Iapichino G, Mascheroni D, et al. Prolonged independent lung respiratory treatment after single lung transplantation in pulmonary emphysema. Chest 1993;103:96–100.
16. Popple C, Higgins T, McCarthy P, et al. Unilateral auto-PEEP in the recipient of a single lung transplant. Chest 1993;103:297–9.
17. Officer TM, Wheeler DR, Frost AE, Rodarte JR. Respiratory control during independent lung ventilation. Chest 2001;120:678–81.
18. Pinsky DJ, Naka Y, Chowdhury NC, et al. The nitric oxide/cyclic GMP pathway in organ transplantation:

critical role in successful lung preservation. Proc Natl Acad Sci USA 1994;91:12086–90.
19. Yamashita MR, Schmid A, Ando K, Cooper JD, Patterson GA. Nitroprusside ameliorates lung allograft reperfusion injury. Ann Thorac Surg 1996;62:791–6.
20. Bacha EA, Herve P, Murakami S, et al. Lasting beneficial effect of short term inhaled nitric oxide on graft function after lung transplantation. Paris-Sud University Lung Transplantation Group. J Thorac Cardiovasc Surg 1996; 112:590–8.
21. Naka YN, Chowdhury NC, Ox MC, et al. Nitroglycerin maintains graft vascular homeostasis and enhances preservation in an orthotopic rat lung transplant model. J Thorac Cardiovasc Surg 1995;109:206–10.
22. Bacha EA, Sellak H, Murakami S, et al. Inhaled nitric oxide attenuates reperfusion injury in non-heart beating-donor lung transplantation. Paris-Sud University Lung Transplantation Group. Transplantation 1997; 63:1380–6.
23. Karamsetty MR, Klinger JR. NO: more than just a vasodilator in lung transplantation. Am J Respir Cell Mol Biol 2002;26:1–5.
24. Ricagna F, Miller VM, Tazelaar HD, McGregor CG. Endothelin-1 and cell proliferation in lung organ cultures: implications for lung allografts. Transplantation 1996;62:1492–8.
25. Minamoto K, Pinsky DJ, Fuijita T, Naka Y. Timing of nitric oxide donor supplementation determines endothelin-1 regulation and quality of lung preservation for transplantation. Am J Respir Cell Mol Biol 2002;26: 14–21.
26. Bhabra MS, Hopkinson DN, Shaw TE, Hooper TL. Low dose nitric oxide inhalation during initial reperfusion enhances rat lung graft function. Ann Thorac Surg 1997;63:339–44.
27. Struber M, Harringer W, Ernest M, et al. Inhaled nitric oxide as a prophylactic treatment against reperfusion injury of the lung. Thorac Cardiovasc Surg 1999;47: 179–82.
28. Meade MO, Granton JT, Matte-Martyn A, et al. A randomized trial of inhaled nitric oxide to prevent ischemia–reperfusion injury after lung transplantation. Am J Respir Crit Care Med 2003;167:1483–9.
29. Ardehali A, Laks H, Levine M, et al. A prospective trail of inhaled nitric oxide in clinical lung transplantation. Transplantation 2001;72:112–5.
30. Cornfield DN, Milla CE, Hadda IY, Barbato JE, Park SJ. Safety of inhaled nitric oxide after lung transplantation. J Heart Lung Transplant 2003;22:903–7.
31. Date H, Triantafillou AN, Trulock EP, et al. Inhaled nitric oxide reduces human lung allograft dysfunction. J Thorac Cardiovasc Surg 1996;111:913–9.
32. Adatia I, Lillehei C, Arnold JH, et al. Inhaled nitric oxide in the treatment of postoperative graft dysfunction after lung transplantation. Ann Thorac Surg 1994;57:1311–8.
33. MacDonald P, Mundy J, Rogers P, et al. Successful treatment of life-threatening acute reperfusion injury after lung transplantation with inhaled nitric oxide. J Thorac Cardiovasc Surg 1995;110:861–3.
34. Garat C, Jayr C, Eddahibi S, et al. Effects of inhaled nitric oxide or inhibition of endogenous nitric oxide formation on hypoxic lung injury. Am J Respir Crit Care Med 1997;155:1957–64.
35. Taylor RW, Zimmerman JL, Dellinger RP, et al. Low-dose inhaled nitric oxide in patients with acute lung injury. JAMA 2004;291:1603–9.
36. Sokol J, Jacobs SF, Bohn D. Inhaled nitric oxide for acute hypoxemic respiratory failure in children and adults. Cochrane Database Syst Rev 2003; CD002787.
37. Vainikka TL, Heikkila LJ, Kukkonen S, Toivonen HJ. Inhaled NO and prostacyclin during porcine single lung transplantation. Ann Thorac Surg 2001;72:1892–7.
38. Murakami S, Bacha EA, Mazmanian GM, et al. Effects of various timings and concentrations of inhaled nitric oxide in lung ischemia–reperfusion: the Paris-Sud University Lung Transplantation Group. Am J Respir Crit Care Med 1997;156:454–8.
39. Lavoie A, Hall JB, Olson DM, Wylam ME. Life-threatening effects of discontinuing inhaled nitric oxide in severe respiratory failure. Am J Respir Crit Care Med 1996;153: 1985–7.
40. Eppinger MJ, Ward PA, Jones ML, Bolling SF, Deeb GM. Disparate effects of nitric oxide on lung ischemia–reperfusion injury. Ann Thorac Surg 1995;60:1169–76.
41. Chiang CH, Wu K, Yu CP, et al. Protective agents used as additives in University of Wisconsin solution to promote protection against ischaemia–reperfusion injury in rat lung. Clin Sci (Lond) 1998;95:369–76.
42. Chiang CH, Wu K, Yu CP, et al. Hypothermia and prostaglandin E(1) produce synergistic attenuation of ischemia–reperfusion lung injury. Am J Respir Crit Care Med 1999;160:1319–23.
43. Naka Y, Roy DK, Liao H, et al. cAMP-mediated vascular protection in an orthotopic rat lung transplant model. Insights into the mechanism of action of prostaglandin E1 to improve lung preservation. Circ Res 1996; 79:773–83.
44. Levin G, Duffin KL, Obukowicz MG, et al. Differential metabolism of dihomo-gamma-linolenic acid and arachidonic acid by cyclo-oxygenase-1 and cyclo-oxygenase-2: implications for cellular synthesis of prostaglandin E1 and prostaglandin E2. Biochem J 2002;365:489–96.
45. Aoe M, Trachiotis GD, Okabayashi K, et al. Administration of prostaglandin E1 after lung transplantation improves early graft function. Ann Thorac Surg 1994;58: 655–61.
46. DeCampos KN, Keshavjee S, Liu M, Slutsky AS. Prevention of rapid reperfusion-induced lung injury with prostaglandin E1 during the initial period of reperfusion. J Heart Lung Transplant 1998;17:1121–8.
47. Matsuzaki Y, Waddell TK, Puskas JD, et al. Amelioration of post-ischemic lung reperfusion injury by prostaglandin E1. Am Rev Respir Dis 1993;148:882–9.
48. de Perrot M, Fischer S, Liu M, et al. Prostaglandin E1 protects lung transplants from ischemia–reperfusion injury: a shift from pro- to anti-inflammatory cytokines. Transplantation 2001;72:1505–12.
49. Okada Y, Marchevsky AM, Zuo XJ, et al. Accumulation of platelets in rat syngeneic lung transplants: a potential

factor responsible for preservation–reperfusion injury. Transplantation 1997;64:801–6.
50. Koga T, Az-ma T, Yuge O. Prostaglandin E1 at clinically relevant concentrations inhibits aggregation of platelets under synergic interaction with endothelial cells. Acta Anaesthesiol Scand 2002;46:987–93.
51. Okada Y, Marchevsky AM, Kass RM, Matloff JM, Jordan SC. A stable prostacyclin analog, beraprost sodium, attenuates platelet accumulation and preservation–reperfusion injury of isografts in a rat model of lung transplantation. Transplantation 1998;66:1132–6.
52. Fiser SM, Cope JT, Kron IL, et al. Aerosolized prostacyclin (epoprostenol) as an alternative to inhaled nitric oxide for patients with reperfusion injury after lung transplantation. J Thorac Cardiovasc Surg 2001;121: 981–2.
53. Schutte H, Lockinger A, Seeger W, Grimminger F. Aerosolized PGE1, PGI2 and nitroprusside protect against vascular leakage in lung ischaemia–reperfusion. Eur Respir J 2001;18:15–22.
54. Schutte H, Schell A, Schafer C, et al. Subthreshold doses of nebulized prostacyclin and rolipram synergistically protect against lung ischemia–reperfusion. Transplantation 2003;75:814–21.
55. Weaver TE, Whitsett JA. Structure and function of pulmonary surfactant proteins. Semin Perinatol 1988;12: 213–20.
56. Novick RJ, Possmeyer F, Veldhuizen RAW, et al. Surfactant analysis and replacement therapy: a future tool of the lung transplant surgeon? Ann Thorac Surg 1991;52: 1194–200.
57. King JR. Pulmonary surfactant. J Appl Physiol 1982;53: 1–8.
58. Ochs M, Nenadic I, Fehrenbach A, et al. Ultrastructural alterations in intraalveolar surfactant subtypes after experimental ischemia and reperfusion. Am J Respir Crit Care Med 1999;160:718–24.
59. Waldhausen JA, Giammona ST, Kilmann JW, et al. Effect of transplantation of canine lung on pulmonary compliance and surfactant. JAMA 1965;191:1002–5.
60. Andrade R, Solien EE, Wangensteen OD. Surfactant dysfunction in lung preservation. Transplantation 1995; 60:536–41.
61. Hohlfeld JM, Tiryaki E, Hamm H, et al. Pulmonary surfactant activity is impaired in lung transplant recipients. Am J Respir Crit Care Med 1998;158:706–12.
62. Ochs M, Fehrenbach H, Nenadic I, et al. Preservation of intraalveolar surfactant in a rat lung ischaemia/reperfusion injury model. Eur Respir J 2000;15:526–31.
63. Veldhuizen RA, Lee J, Sandler D, et al. Alterations in pulmonary surfactant composition and activity after experimental lung transplantation. Am Rev Respir Dis 1993;148:208–15.
64. Novick RJ, Veldhuizen RA, Possmayer F, et al. Exogenous surfactant therapy in thirty-eight hour lung graft preservation for lung transplantation. J Thorac Cardiovasc Surg 1994;108:259–68.
65. Maitra G, Inchley K, Novick RJ, et al. Acute lung injury and lung transplantation influence in vitro subtype conversion of pulmonary surfactant. Am J Physiol Lung Cell Mol Physiol 2002;282:L67–74.
66. Novick RJ, Gilpin AA, Gehman KE, et al. Mitigation of injury in canine lung grafts by exogenous surfactant therapy. J Thorac Cardiovasc Surg 1997;113:342–53.
67. Hohlfeld JM, Struber M, Ahlf K, et al. Exogenous surfactant improves survival and surfactant function in ischaemia–reperfusion injury in minipigs. Eur Respir J 1999; 5:1037–43.
68. Erasmus ME, Hofstede GJ, Petersen AH, et al. SP-A enriched surfactant for treatment of rat lung transplant with SP-A deficiency after storage and reperfusion. Transplantation 2002;73:348–52.
69. de Perrot M, Liu M, Wadell TK, Keshavjee S. Ischemia–reperfusion-induced lung injury. Am J Respir Crit Care Med 2003;167:490–511.
70. Erasmus ME, Petersen AH, Hofstede G, et al. Surfactant treatment before reperfusion improves immediate function of lung transplants in rats. Am J Respir Crit Care Med 1996;153:665–70.
71. Hausen B, Rohde R, Hewitt CW, et al. Exogenous surfactant treatment before and after sixteen hours of ischemia in experimental lung transplantation. J Thorac Cardiovasc Surg 1997;113:1050–8.
72. Novick RJ, MacDonald J, Veldhuizen RAW, et al. Evaluation of surfactant treatment strategies after prolonged graft storage in lung transplantation. Am J Respir Crit Care Med 1996;154:98–104.
73. Koletsis E, Chatzimichalis A, Fotopoulos V, et al. Donor lung pretreatment with surfactant in experimental transplantation preserves graft hemodynamics and alveolar morphology. Exp Biol Med 2003;228:540–5.
74. Strueber M, Cremer J, Harringer W, et al. Nebulized synthetic surfactant in reperfusion injury after single lung transplantation. J Thorac Cardiovasc Surg 1995; 110:563–4.
75. Strueber M, Hirt SW, Cremer J, et al. Surfactant replacement in reperfusion injury after clinical lung transplantation. Intensive Care Med 1999;25:862–4.
76. Strueber M. What is the role of surfactant and inhaled nitric oxide in lung transplantation? Crit Care 2002;6: 186–7.
77. Strueber M, Niedermeyer J, Warnecke G, et al. Exogenous surfactant instillation in lung donors to reduce early graft dysfunction. J Heart Lung Transplant 2003; 22(suppl):S14.
78. Pierre AF, Xavier AM, Liu M, et al. Effect of complement inhibition with soluble complement receptor 1 on pig allotransplant lung function. Transplantation 1998;66: 723–32.
79. Schmid RA, Zollinger A, Singer T, et al. Effect of soluble complement receptor type 1 on reperfusion edema and neutrophil migration after lung allotransplantation in swine. J Thorac Cardiovasc Surg 1998;116:90–7.
80. Strüber M, Hagl C, Hirt SW, et al. C1-esterase inhibitor in graft failure after lung transplantation. Intensive Care Med 1999;25:1315–8.
81. Zamora MR, Davis RD, Keshavjee SH, et al. Complement inhibition attenuates human lung transplant reperfusion injury: a multicenter trial. Chest 1999;116(suppl):46S.

82. Keshavjee S, Davis RD, Zamora MR, de Perrot M, Patterson GA. A randomized, placebo controlled trial of complement inhibition in ischemia–reperfusion injury after lung transplantation in human beings. J Thorac Cardiovasc Surg 2005;129:423–8.
83. Wittwer t, Grote M, Oppelt P, et al. Impact of PAF antagonist BN 52021 (Ginkolide B) on post-ischemic graft function in clinical lung transplantation. J Heart Lung Transplant 2001;20:358–63.
84. Grino JM. BN 52021: a platelet activating factor antagonist for preventing post-transplant renal failure: a double-blind, randomized study: the BN 52021 study group in renal transplantation. Ann Intern Med 1994;121: 345–7.
85. Fisher S, Maclean AA, Liu M, Kalirai B, Keshavjee SH. Inhibition of angiotensin-converting enzyme by captopril: a novel approach to reduce ischemia–reperfusion injury after lung transplantation. J Thorac Cardiovasc Surg 2000;120:573–80.
86. Salvatierra A, Guerrero R, Rodriguez M, et al. Antithrombin III prevents early pulmonary dysfunction after lung transplantation in the dog. Circulation 2001;104:2975–80.
87. Soccal PM, Gasche Y, Miniati DN, et al. Matrix metalloproteinase inhibitor decreases ischemia–reperfusion injury after lung transplantation. Am J Transplant 2004;4: 41–50.
88. Eriksson LT, Steen S. Induced hypothermia in critical respiratory failure after lung transplantation. Ann Thorac Surg 1998;65:827–9.
89. Eriksson LT, Roscher R, Ingemansson R, Steen S. Cardiovascular effects of induced hypothermia after lung transplantation. Ann Thorac Surg 1999;67:804–9.
90. Stolar CJH, Snedecor SM, Bartlett RH. Extracorporeal membrane oxygenation and neonatal respiratory failure: experience from the extracorporeal life support organization. J Pediatr Surg 1991;26:563–71.
91. Kolla S, Awad SS, Rich PB, et al. Extracorporeal life support for 100 adult patients with severe respiratory failure. Ann Surg 1997;226:544–66.
92. Meyers BF, Sundt TM III, Henry S, et al. Selective use of extracorporeal membrane oxygenation is warranted after lung transplantation. J Thorac Cardiovasc Surg 2000; 120:20–6.
93. Fiser SM, Kron IL, Long SM, et al. Early intervention after severe oxygenation index elevation improves survival following lung transplantation. J Heart Lung Transplant 2001;20:631–6.
94. Glassman LR, Keenan RJ, Fabrizio MC, et al. Extracorporeal membrane oxygenation as an adjunct treatment for primary graft failure in adult lung transplant recipients. J Thorac Cardiovasc Surg 1995;110:723–7.
95. Ball JW Jr, Noon GP, Short HD, Scheinin SA. Extracorporeal membrane oxygenation for early graft dysfunction in lung transplantation: a case report. J Heart Lung Transplant 1997;16:468–71.
96. Smedira NG, Moazami N, Golding CM, et al. Clinical experience with 202 adults receiving extracorporeal membrane oxygenation for cardiac failure: survival at five years. J Thorac Cardiovasc Surg 2001;122:92–102.
97. Kato J, Seo T, Ando H, Takagi H, Takahiro I. Coronary arterial perfusion during venoarterial extracorporeal membrane oxygenation. J Thorac Cardiovasc Surg 1996; 111:630–6.
98. Sekela ME, Noon GP, Holland VA, Lawrence EC. Differential perfusion: potential complication of femoral–femoral bypass during lung transplantation. J Heart Lung Transplant 1991;10:322–4.
99. Pereszlenyi A, Lang G, Steltzer H, et al. Bilateral lung transplantation with intra- and postoperatively prolonged ECMO support in patients with pulmonary hypertension. Eur J Cardio-thorac Surg 2002;21:858–63.
100. Nelems JM, Duffin J, Glynn MFX, et al. Extracorporeal membrane oxygenator support for human lung transplantation. J Thorac Cardiovasc Surg 1978;76:28–32.
101. Jurmann MJ, Haverich A, Demertzis S, et al. Extracorporeal membrane oxygenation (ECMO): extended indications for artificial support of both heart and lungs. Int J Artif Org 1991;14:771–4.
102. Zenati M, Pham SM, Keenan RJ, Griffith BP. Extracorporeal membrane oxygenation for lung transplant recipients with primary severe donor lung dysfunction. Transplant Int 1996;9:227–30.
103. Nguyen DQ, Kulick DM, Bolman RM III, et al. Temporary ECMO support following lung and heart–lung transplantation. J Heart Lung Transplant 2000;19:313–6.
104. Horowitz JH, Carrico CJ, Shires T. Pulmonary response to major injury. Arch Surg 1974;108:349–55.
105. Ko WJ, Chen YS, Luh SP, Chu SH. Extracorporeal membrane oxygenation support for single-lung transplantation in patients with primary pulmonary hypertension. Transplant Proc 1999;31:166–8.
106. Ko WJ, Chen YS, Lee YC. Replacing cardiopulmonary bypass with extracorporeal membrane oxygenation in lung transplantation operations. Artif Organs 2001;25: 607–12.
107. Dahlberg PS, Prekker ME, Hertz MI, Herrington CS, Park SJ. Medium term results of ECMO for severe acute lung injury following lung transplantation. J Heart Lung Transplant 2003;22(suppl 1):S159–60.
108. Trulock EP, Edwards LB, Taylor DO, et al. The registry of the International Society for Heart and Lung Transplantation: twentieth official adult lung and heart–lung transplant report—2003. J Heart Lung Transplant 2003;22: 625–35.
109. Wekerle T, Klepetko W, Wisser W, et al. Lung retransplantation: institutional report on a series of twenty patients. J Heart Lung Transplant 1996;15:182–9.
110. Schäfers HJ, Hausen B, Wahlers T, et al. Retransplantation of the lung. A single center experience. Eur J Cardiothorac Surg 1995;9:291–6.
111. Haverich A, Hirt SW, Wahlers T, et al. Functional results after lung retransplantation. J Heart Lung Transplant 1994;13:48–55.
112. Novick RJ, Stitt L. Pulmonary retransplantation. Semin Thorac Cardiovasc Surg 1998;10:227–36.
113. Novick RJ, Stitt LW, Al Kattan K, et al. Pulmonary retransplantation: predictors of graft function and survival in 230 patients. Pulmonary Retransplant Registry. Ann Thorac Surg 1998;65:227–34.

114. Novick RJ, Stitt L, Schafers HJ, et al. Pulmonary retransplantation: does the indication for operation influence postoperative lung function? J Thorac Cardiovasc Surg 1996;112:1504–13.
115. Novick RJ, Schafers HJ, Stitt L, et al. Seventy-two pulmonary re-transplantations for obliterative bronchiolitis: predictors of survival. Ann Thorac Surg 1995;60:111–6.
116. Novick RJ, Kaye MP, Patterson GA, et al. Redo lung transplantation: a North American–European experience. J Heart Lung Transplant 1993;12:5–16.
117. Novick RJ, Schäfers HJ, Stitt L, et al. Recurrence of obliterative bronchiolitis and determinants of outcome in 139 pulmonary retransplant recipients. J Thorac Cardiovasc Surg 1995;110:1402–14.