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

Marc de Perrot, MD,[a] Robert S. Bonser, MSBCh, FRCS,[b] John Dark, MB, FRCS,[c] Rosemary F. Kelly, MD,[d] David McGiffin, MD,[e] Rebecca Menza, RN,[f] Octavio Pajaro, MD, PhD,[g] Stephan Schueler, MD,[c] and Geert M. Verleden, MD, PhD[h]

Primary graft dysfunction is the end result of a series of donor lung injuries before and after the declaration of brain death and during the transplant process, as well as in the recipient after reperfusion.[1] Donor factors play an important role in the development of primary graft dysfunction after lung transplantation, but few clinical studies have analyzed their impact. Results have been hindered by variations in donor selection criteria and by use of different definitions of primary graft dysfunction between centers. The impact of donor factors, however, appears predominant during the initial 24 hours of reperfusion, whereas recipient factors seem more important thereafter.[2] The impact of donor factors can be differentiated into those that are inherent to lung donor characteristics and those that are acquired at the time of death or later. This distinction is important because adequate donor management could potentially influence factors that are acquired at the time of death or subsequent to death.

INHERENT LUNG DONOR CHARACTERISTICS

Age, smoking history, race, gender and underlying lung disease are inherent donor characteristics that may influence the quality of the lungs and potentially impact on recipient outcome. Christie and colleagues analyzed the impact of donor factors in a cohort study of 255 consecutive lung transplants and observed that several donor factors, including female gender, African American ethnicity and age, had an independent impact on the development of primary graft dysfunction.[3] The difference seen in graft outcome with donor female gender has been observed in other organ transplantations and may be due to size discrepancies between donor and recipient, although other factors, such as gender-linked antigens, cannot be excluded. Because the mechanisms by which race and gender impact on outcome after lung transplantation remain speculative, they should not be used in the decision to accept or reject a donor lung.

Christie and colleagues found that donor age had an independent impact on the development of primary graft dysfunction after lung transplantation. Donor ages >45 years and <21 years were associated with a higher risk of primary graft dysfunction. Although the data for the young donors are equivocal, similar findings have been observed in the UNOS/ISHLT registry for older donors.[4] Indeed, the combination of donor age >45 years and ischemic time >7 to 8 hours had a significant impact on 30-day mortality after lung transplantation, according to registry data.[4] Some groups, however, have successfully used older donors if all other selection criteria were ideal.[5–9] Hence, use of older donors most likely increases the risk of primary graft dysfunction, but the risk seems limited in the absence of other risk factors.

The impact of smoking history on primary graft dysfunction remains controversial. Although Oto and colleagues recently reported that a cumulative smoking history of >20 pack-years is associated with prolonged mechanical ventilation and ICU stay after lung transplantation, the incidence of death from non-specific graft failure was not significantly different between donors with a smoking history of >20 vs <20 pack-years.[10] Unfortunately, these investigators did not directly report the impact of donor smoking history on the incidence of primary graft dysfunction. In their analysis, Christie and colleagues, observed that donor smoking history had no significant impact on primary graft dysfunction after lung transplantation. In the future, analysis in larger groups of patients will be necessary to quantify more precisely the impact that donor smoking history may play on the development of primary graft dysfunction.

ACQUIRED LUNG DONOR FACTORS

The occurrence of brain death, prolonged mechanical ventilation, bronchoaspiration, pneumonia, trauma,

From the [a]Toronto General Hospital, Toronto, Ontario, Canada; [b]Queen Elizabeth Hospital, Birmingham, UK; [c]Freeman Hospital, Newcastle upon Tyne, UK; [d]University of Minnesota, Minneapolis, Minnesota; [e]University of Alabama, Birmingham, Alabama; [f]University of California, Berkeley, California; [g]Mayo Clinic Jacksonville, Jacksonville, Florida; and [h]University Hospitals Leuven, Leuven, Belgium.

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Reprint requests: Marc de Perrot, MD, Division of Thoracic Surgery, Toronto General Hospital, 9N-961, 200 Elizabeth Street, Toronto, ON M5G 2C4, Canada. Telephone: 416-340-6120. Fax: 416-340-4556. E-mail: marc.deperrot@uhn.on.ca

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multiple blood transfusions or hemodynamic instability in the donor before the retrieval procedure can potentially contribute to lung injury and primary graft dysfunction.[11]

The deleterious effect of brain death on organ function has been increasingly recognized over the last few years.[12] Brain death can induce disruption in homeostatic regulation, with profound disturbances in endocrine function, and an intense inflammatory reaction that may reduce the tolerance of the organs to handle a period of ischemia.[13] Brain death has also been demonstrated experimentally to increase the risk of acute rejection and chronic graft dysfunction.[14,15] Clinically, Sommers and colleagues observed that recipients from donors with closed head injury had significantly lower oxygenation on arrival in the ICU than recipients from donors with other causes of death.[2] Other groups, however, did not confirm this finding.[3,16]

Biopsies from cadaveric kidney donors have been shown to have higher levels of inflammatory cytokines, adhesion molecules and human leukocyte antigen-DR (HLA-DR) than biopsies from living donors, and the expression of these markers on tubular cells before transplantation was associated with a higher incidence of primary graft dysfunction and early acute rejection.[17,18] Fisher and colleagues showed that interleukin-8 (IL-8) in lung bronchoalveolar lavage from 28 nontraumatic brain-dead donors was significantly higher than in healthy controls, and these IL-8 levels correlated with neutrophil infiltration in donor lung tissue.[19]

Several groups have begun to administer a bolus of steroids (methylprednisolone ~15 mg/kg) after brain-death declaration to all potential lung donors to reduce the inflammatory reaction induced by brain death. The steroid bolus has been shown to improve arterial oxygen tension in the donor and also to be associated with an increased lung donor recovery rate as well as improved lung function in the recipient after transplantation.[20–22]

Hemodynamic instability with persistent low blood pressures can increase the risk of post-operative graft dysfunction after kidney and liver transplantation.[23,24] Prolonged hypotension before death has also been shown to be associated with significant deterioration in lung graft function after reperfusion in a rat model of non–heart-beating donor.[25] Although not studied in clinical lung transplantation, similar findings are to be expected, because adequate blood pressure and stable hemodynamic parameters are important to maintain optimal oxygen delivery and energy metabolism in organ tissues.

Optimal filling pressures have not been analyzed in humans after brain-death declaration. However, experiments with brain-dead pigs have shown that the heart dilates rapidly and fails with a central venous pressure (CVP) of >9 mm Hg.[26] A CVP of <10 mm Hg is usually recommended in clinical practice. However, caution must be taken with fluid resuscitation in brain-dead donors because excessive fluid administration can cause rapid deterioration in lung function, even if the CVP remains at <10 mm Hg.[27] Excessive fluid administration can be detrimental to the lung, particularly if left-heart dysfunction has been demonstrated.

Persistent hypotension and hemodynamic instability from cardiac dysfunction are best managed with vasopressors. Dopamine is used as a first choice because of its potential vasodilative effect on renal and mesenteric blood flow. In addition, low-dose dopamine has recently been shown to improve lung edema in brain-dead donors.[28] Although the data are limited, there is relatively strong evidence suggesting that epinephrine and norepinephrine should be replaced with vasopressin. Vasopressin has been shown to have a stabilizing effect on systemic blood pressure after brain death while also allowing for reduction or discontinuation of epinephrine and norepinephrine in most cadaveric donors.[29–31] In addition, vasopressin improves maintenance of energy metabolism and is effective against diabetes insipidus, which occurs in 80% of brain-dead donors.[32] Although dopamine and vasopressin are helpful in donor management, their impact on recipient outcome remains to be demonstrated.

Because pneumonia has been a major cause of early morbidity and mortality in lung transplant recipients, utilization of lungs from donors with a positive gram stain in tracheal secretions has initially been avoided. However, aggressive antibiotic treatment in donors and recipients has significantly reduced the incidence of recipient pneumonia, and recent series have shown that gram stain of donor tracheal aspirates does not correlate with recipient outcome.[33] Positive gram stain of tracheal aspirates most likely does not indicate ongoing pneumonia, but simply a collection of purulent secretions in the upper airways. In contrast, positive cultures from donor bronchoalveolar lavage (BAL) may indicate ongoing pneumonia, be associated with lower oxygenation after reperfusion in the recipient, and lead to longer ICU stay as well as prolonged ventilation when compared to donors with negative BAL bacterial cultures.[34] BAL cultures should be taken from all donors to aggressively adapt the anti-biotherapy post-operatively.

DONOR SELECTION

Clinical Markers

The current criteria used to assess donor lungs are based on donor history, arterial blood gases, chest X-ray appearance, bronchoscopy findings and physical examination of the lung at the time of retrieval. These criteria have been reviewed in detail previously and are not the primary focus of this study.[35] However, their accuracy

in determining the risk of primary graft dysfunction after transplantation is not optimal. Primary graft dysfunction occasionally occurs in patients receiving lungs from ideal donors, whereas extended donors have been used without significant impairment in post-operative lung function.[4–7]

Biologic Markers

Because clinical factors are not accurate enough in predicting primary graft dysfunction after lung transplantation, some groups have focused on biologic markers as a predictor of outcome. As mentioned previously, kidney biopsies from cadaveric kidney donors appear to have significantly higher levels of inflammatory cytokines, adhesion molecules and HLA-DR than biopsies from living donors, and the expression of these markers on tubular cells before transplantation can be associated with a higher incidence of primary graft dysfunction and early acute rejection after transplantation.[17,18] In human lung transplantation, the chemokine IL-8 is upregulated in BAL and lung tissue from brain-dead donors and the level seems to correlate with the incidence of primary graft dysfunction after reperfusion.[36,37]

Biologic markers should be accurate, provide rapid results, and be readily available for clinical use. Rapid, quantitative reverse transcriptase–polymerase chain reaction (RT-PCR) may provide some of these advantages, such as measurement of cytokine levels within 1 hour after lung biopsy. The demonstration of tumor necrosis factor-alpha by RT-PCR in donor myocardium was found to predict post-operative right-heart dysfunction in recipients after heart transplantation.[38] In clinical lung transplantation, the level of IL-6 measured by RT-PCR and the ratio of the pro-inflammatory cytokine, IL-6, to the anti-inflammatory cytokine, IL-10, was found to predict 30-day mortality and mortality from primary graft dysfunction, whereas no clinical factor did so in the same group of patients.[39] In the future, rapid analysis of pro- and anti-inflammatory markers in lung parenchyma may be extremely useful to reduce the incidence of primary graft dysfunction by determining more precisely the type of lung suitable for transplantation or by influencing post-implantation management.

Lung Preservation

Ischemia–reperfusion-induced lung injury plays a major role in the development of primary graft dysfunction. It is an inevitable step in the transplant process that may potentially add to other injuries occurring in the donor before the period of ischemia or in the recipient after reperfusion. Much of the experimental work over the past decade has focused on how to optimize the methods of lung preservation to reduce the impact of ischemia–reperfusion injury on post-transplant lung function. The temperature, volume and pressure of the preservation solution as well as inflation, temperature and oxygenation of the lung during storage have all been shown experimentally to impact on the quality of the lung after reperfusion. In addition, the type of lung preservation used and use of a retrograde flush have been shown experimentally and clinically to improve post-operative lung function. Some of these experiments are briefly reviewed in what follows.

Methods of Preservation

The current clinical practice of lung preservation is a hypothermic pulmonary artery flush at 50 to 60 ml/kg, coupled with topical cold saline solution while ventilating the lungs.[40] The lungs are then transported inflated, in a hypothermic (4°C) solution. The lungs are perfused via the pulmonary artery to uniformly cool the lung tissue and remove blood from the pulmonary vascular bed. Flushing prevents vessel thrombosis and insures uniform tissue cooling, which then decreases membrane damage from retained macrophages and neutrophils.[41]

Temperature of Preservation Solution

Historically, hypothermia has been a major component of lung preservation and continues to play an important role.[42] Hypothermia suppresses the activity of cellular degradative enzymes, which would otherwise lead to a rapid loss of cellular viability during ischemia at normothermic temperatures. Preservation of tissues at low temperatures reduces metabolic activity to such a level that cell viability can be maintained in the face of ischemia.[43] Lung preservation at 4°C decreases the metabolic rate to 5% of the metabolic rate at 37°C.

Controversy remains regarding the optimal flush temperature for lung preservation. Small animal studies suggest that warmer preservation solution temperature would be better than 4°C.[44,45] However, ultrastructural analyses of human lung parenchyma at various timepoints during the preservation period demonstrate minimal lung injury despite preservation at 4°C.[46,47] Hence, the known advantage of reduced metabolic activity at 4°C and technical ease of maintaining this temperature keeps the use of hypothermic perfusion flush temperature at 4°C the standard flushing temperature.

Volume of Preservation Solution

The amount of flush solution required to adequately clear the blood from the lungs and optimize graft function is dependent on patient size and perfusion flow rates. Haverich and colleagues found that a solution volume of 60 ml/kg given at a high flow rate improved lung cooling and post-operative lung function.[48] Although Steen and colleagues recommended volumes as high as 150 ml/kg, this has not been widely

adopted as a significant improvement over 60 ml/kg.[49] The infusion of 60 ml/kg of perfusate solution is sufficient to clear the lungs of blood and uniformly cool the lungs as well. If infused at a low perfusion pressure, the infusion requires only several minutes to complete.

Pressure of Preservation Solution Infusion

The optimal pulmonary artery pressure for infusion is controversial. Sasaki and colleagues observed that flushing pressures of 10 to 15 mm Hg achieved significantly better lung function than infusions at pressures of 20 and 25 mm Hg.[50] The high pulmonary artery pressures noted during the flush with Euro-Collins solution and the improvement in lung function with the addition of prostaglandins also suggest that the optimal perfusion pressure should be in the lower range to maximize graft function after transplantation.[51]

Inflation or Ventilation

Experimental and clinical studies clearly support the importance of ventilation during lung procurement and inflation during storage.[41,52] However, over-distension of the lung by either static inflation, high tidal volume or high positive end-expiratory pressure (PEEP) can be detrimental to the lungs, and hyperinflation during storage can increase the pulmonary capillary filtration coefficient.[53] Lung inflation during storage should be limited to 50% of the total lung capacity or to an airway pressure of 10 to 15 cm H_2O to avoid barotraumas.[54,55]

Storage Temperature

The ideal temperature for lung storage remains unclear. In the process of lung transportation, hypothermia is used to decrease cellular metabolic activity and preserve lung function. However, it can also compound injury due to ischemia–reperfusion. Tissue edema as a result of hypothermia is due to decreased ATPase activity.[56] ATPase-dependent ion balance in the cell becomes disrupted, alters cellular function, and leads to membrane disruption, followed by cell death. The ATPase activity is temperature-dependent and tissue-specific.[56] In the lung, hypothermia results in increased extravascular fluid and pulmonary vasoconstriction. This contributes to diminished oxygen exchange and increased pulmonary vascular resistance after reperfusion. Several animal studies have shown that pulmonary function after 12 to 24 hours of storage is superior if the lungs are preserved at 10°C instead of 4°C or 15°C.[57] However, in clinical lung transplantation, parenchymal injury is dependent on multiple factors, making it difficult to determine the precise contribution from hypothermia alone. In addition, lungs preserved at 10°C require a greater amount of metabolic substrate and the risk of lung injury can increase extremely rapidly if the temperature rises above 10°C during preservation. Hence, given the logistics of transportation and the inconclusive experimental data regarding optimal storage temperature, 4°C continues to be the most common temperature for lung storage.

Oxygenation

The lung has the ability to remain in aerobic conditions during preservation if it is inflated with oxygen.[58] This remains true even under conditions of hypothermia.[59] However, there is a fine line between oxygen requirements for metabolic purposes, and excessive concentrations leading to free-radical production even before reperfusion. In fact, oxygen-free-radical–mediated injury has been shown to occur before reperfusion when rabbit lungs were stored at 10°C, and inflated with 100% oxygen.[60] This correlates with the finding in rat lungs that there is an oxygen-dependent injury taking place during the ischemic phase.[61] As a result, the most common clinical practice is ventilation and lung inflation with an F_{IO_2} of 0.30 to 0.50.

Preservation Solutions

There has been a recent trend toward the use of low-potassium solutions (extracellular), such as Perfadex (Vitrolife, Goteborg, Sweden), for lung preservation. Low-potassium dextran solution has been introduced in the clinical arena after a significant amount of experimental work illustrated its benefits.[49,62] Low-potassium dextran (LPD) is the only preservation solution developed specifically for lung preservation. Other low-potassium solutions include Wallwork's solution and Celsior. Celsior contains the anti-oxidants mannitol, glutathione, glutamate and histidine as well as lactobionate. A modified cold blood solution as proposed by Wallwork and colleagues includes the addition of heparin and lactated Ringer solution to the blood.

The key components of LPD are the dextran and low-potassium concentration. Dextran-40 in the LPD solution functions as an oncotic agent, tending to keep water in the intravascular compartment, and thereby decreasing interstitial edema formation. It also reduces the aggregation of erythrocytes and circulating thrombocytes, which may improve the microcirculation and reduce cellular activation. The low-potassium concentration maintains normal pulmonary artery pressures during infusion. A further development is a dextran–glucose-based extracellular solution.[63,64] The addition of glucose is designed to support aerobic metabolism and maintain cell integrity during prolonged ischemia. Perfadex is an LPD–glucose solution that is now clinically available worldwide.

The addition of glucose to a lung preservation solution takes advantage of the unique aspect of lung physiology in transplantation. That is, the inflated lung has the ability to supply oxygen to its parenchyma even

during storage. A lung flushed with 1% glucose added to LPD solution and stored for >24 hours was found to be associated with continued normal glucose metabolism in the lung.[63] Analyzing lung tissue, the investigators found that tissue glucose, glucose-6-phosphate and lactate levels rose in a parallel fashion, indicating the presence of glycolysis in response to glucose in the LPD solution.

Clinical reports from 6 centers have compared the effect of Perfadex with an historical control group of lungs preserved with Euro-Collins.[65–70] Five centers showed significantly better lung function on arrival in the ICU and a trend toward lower 30-day mortality with Perfadex. An additional report demonstrated that, after adjustment for graft ischemic time, extracellular-type preservation solutions were associated with a decreased incidence of primary graft dysfunction after lung transplantation when compared with intracellular-type preservation solutions.[71]

Retrograde Flush

Retrograde flush, which refers to the administration of flush solution through the left atrial appendage or the pulmonary veins, and drainage through the pulmonary artery, has been described for lung and heart–lung transplantation. The technique adds the potential advantages of flushing both the bronchial and pulmonary vessels, and of limiting the effect of pulmonary arterial vasoconstriction on the distribution of the flush solution. Experimentally, a retrograde flush has been found to improve lung preservation when compared with an anterograde flush.[72] This effect was attributed to more effective clearance of red blood cells within the capillaries, better distribution of the flush solution along the tracheobronchial tree, and less severe impairment of surfactant function. However, despite the retrograde flush, pre-treatment with prostaglandin E_1 was still helpful in improving pulmonary dynamic compliance after reperfusion.[73] After these results were published, several groups have adopted a combined procedure with an anterograde flush through the pulmonary artery, followed by a retrograde flush through each of the pulmonary veins in situ with the lungs still ventilated. Venuta and colleagues completed a study of 14 patients demonstrating that the addition of a retrograde flush to an anterograde flush was associated with improved lung function after transplantation when compared with an anterograde-only flush.[74] A retrograde flush was also shown to help remove blood clots from the distal pulmonary artery bed that are occasionally seen in cadaveric lung donors.[75,76]

Ischemic Time

Although prolonged ischemic time has been shown by some investigators to have an impact on the occurrence of primary graft dysfunction, its role may have become less important with improvement in lung preservation methods.[77–79] Recently, ischemic times of up to 10 or even 12 hours have been successfully reported with optimal donors, and ischemic times of 6 to 8 hours are usually considered reasonable.[1] Ueno and colleagues reported a series of 74 patients undergoing bilateral lung transplants for indications other than primary pulmonary hypertension and Eisenmenger syndrome, and observed that ischemic times of >8 hours were associated with lower oxygenation in the recipient during the first 24 hours of reperfusion.[80] A large review from the international registry on 5,052 lung transplant recipients has also shown an increased 30-day mortality with cold ischemic times of >7 to 8 hours and donors >45 years of age.[4] However, most of these studies were performed with intracellular preservation solutions such as Euro-Collins, which have been shown to be less efficient than extracellular preservation solutions. Hence, currently, prolonged ischemia should probably be seen as an additional risk factor, but not as a direct cause of primary graft dysfunction.

CONCLUSIONS

Donor factors should be differentiated into those that are inherent to lung donor characteristics and those that are acquired at the time of brain death or thereafter. Inherent lung donor characteristics, such as age and smoking history, can potentially increase the risk of post-operative lung dysfunction. However, improvement in donor management and lung preservation techniques over the past decade have helped to expand the number of lungs available for transplantation and to reduce the risk of primary graft dysfunction. Currently, primary graft dysfunction is more likely to be the end result of a series of insults to the lungs than to be due to a single factor only. In the future, the development of a multi-institutional database prospectively collecting demographic data from lung donors, length of ischemic time and recipient's conditions will help to stratify the impact that each of these factors may have on outcome after lung transplantation. This information as well as the potential development of biologic markers could be extremely helpful to further expand the lung donor pool without increasing the risk of primary graft dysfunction.

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