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Evaluation and Management of the Potential Lung Donor

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SYNOPSIS

The expansion of the donor lung pool has involved an evidence-driven redefinition of acceptable donors. Proceeding with transplantation with an acceptable rather than ideal donor depends on specific patient and organ-related risk factor as well as the severity of recipient illness. Although the physiological optimization of brain dead donors has not changed significantly in recent years, the use of donor management protocols has improved procurement rates. Ex vivo lung perfusion is an increasingly viable strategy to recondition lungs that would otherwise fall below the acceptable threshold for transplant. Ex vivo perfusion trials for preservation of standard donor lungs are ongoing.

Keywords

EVLP; brain death; ex vivo perfusion; lung transplant; organ donor; donor lung management

Introduction

The number of lung transplants in the United States (US) grew by 250% over the last 20 years, from 932 in 1996 to 2,327 in 2016.[1] This dramatic increase, which was mirrored worldwide, was related to advancements in surgical techniques and improvements in immunosuppression and post-transplantation management, making lung transplantation an increasingly attractive treatment option for end-stage lung disease. The proliferation of lung

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transplantation programs, however, would not have been possible without a corresponding expansion of the donor lung pool. This has involved an evidence-driven redefinition of acceptable donors coupled with improved management of potential lung donors and preservation of lung quality following procurement. This review focuses on the current state of donor and donor lung assessment strategies and contemporary techniques for lung preservation prior to transplantation.

Donor evaluation

Historic approaches to evaluating potential lung transplant donors focused on identifying perceived absolute contraindications to donation, leaving a relatively small pool of young donors with no significant medical history, minimal smoking history, and robust pulmonary function (Table 1). As data has emerged on the impact of transplantation from non-ideal—or extended criteria—donors, current donor evaluation is better conceptualized as weighing a constellation of specific risk factors and their impact on post-transplantation allograft function. These variables can be broadly divided into patient specific and organ specific considerations.

Acceptable donors

Smoking—Although non-smokers are ideal and a donor history of cigarette smoking has been associated with primary graft dysfunction (PGD), a large prospective cohort study in the United Kingdom (UK) demonstrated significantly decreased mortality for recipients who received transplants from donors with a smoking history than patients who remained on the waiting list.[2,3] The UK study did not specifically assess post-transplant risk by donor pack-years but a subsequent study in the US showed no increased mortality in single or bilateral lung transplants using donors with >20 pack years.[4,5] Patients who received lungs from actively smoking donors with a >20 pack year history had higher adjusted mortality, however, and smaller cohort studies have suggested higher short- and long-term morality with transplantation from donors with >40 pack-years smoking.[6]

Although smoking cannibals may be a risk factor for donor-acquired fungal infections following transplant, single center cohort studies have not shown an adverse impact of donor inhalational marijuana use.[7]

Age—Large retrospective cohort studies have consistently shown little impact on survival and freedom from bronchiolitis obliterans syndrome (BOS) when using donors 55–65 years of age.[8] A single center study has suggested similar one year mortality with donors >70 years old, although larger cohort studies have found increased mortality with donors older than 65 years, suggesting that utilization of very old donors carries additional risk.[8,9] There are also some combinations of donor and recipient age that may decrease post-transplantation survival. For example, a recent retrospective review found that the use of donors >50 increased the adjusted risk of death for recipients <60 but not those 60 and above.[10]

Other medical history—Although hepatitis C virus (HCV) positive donors have not historically been considered for transplantation to HCV negative recipients, the advent of

direct-acting antiviral drugs against HCV may allow for reassessment of this policy. There is at least one report of an intentional lung transplant of a HCV status mismatch patient successfully treated with direct-acting antiviral drugs.[11] Similarly, a review of United Network of Organ Sharing (UNOS) data on outcomes from anti-hepatitis B core antibody positive donors to hepatitis B non-immune recipients showed no difference in adjusted 1 and 5 year survival, potentially because of the use of prophylactic lamivudine in patients at higher risk for viral transmission.[12]

Several retrospective reviews of the UNOS database have suggested that donor diabetes is a risk factor for lower median and overall survival.[13,14] This finding, however, primarily appears to be driven by increased mortality in single lung transplant recipients suggesting that preference be given to bilateral transplant when considering transplantation from a diabetic donor.[13] It is also unclear whether insulin versus non-insulin-dependent diabetes should impact this decision.

Finally, although there are numerous case reports of donor-transmitted malignancies including melanoma, breast cancer, and glioblastoma multiforme there remains uncertainty as to the tumor type, histopathology, and time from curative intervention that would allow safe transplantation in a donor with a history of malignancy.[15] A recent review of 61 actual donors with unacceptable/high risk of cancer transmission in the UK found no donor-derived cancers, including in 8 lung transplant recipients.[16] Further stratification of risk in specific cancer types may help evaluate whether present guidelines unnecessarily restrict transplantation from donors with very low risk of cancer transmission.

Acceptable lungs

Active infection—Although donor-to-recipient transmission of bacterial and fungal pneumonia is relatively common, occurring in upwards of 50% of cases depending on the donor mechanism of death, donor gram stain characteristics have poor sensitivity and specificity for subsequent recipient pneumonia.[17] The degree of hypoxemia-related to infection is likely a more accurate predictor of organ impairment than the mere presence of an active infection. Prophylactic antibiotic failure is uncommon and appears to be related to the presence of multi-drug resistant bacterial organisms or invasive fungal and mycobacterial donor colonization. When known, transplantation from donors with these infections should be avoided unless a comprehensive post-transplantation antibiotic or antifungal regimen can be identified.[18]

Oxygenation—Historically, the donor arterial partial pressure of oxygen (PaO2) on 100% fraction of inspired oxygen (FiO2) and positive end expiratory pressure (PEEP) 5 has been a critical measure of post-transplant allograft function. The traditional cut-off of a PaO2:FiO2>300 mmHg, however, has not been substantiated in subsequent retrospective reviews. For example, Zafar et al found no additional adjusted mortality for donors in the UNOS database with PaO2 between 200–300 and <200 regardless of single or bilateral transplant.[19] Subsequent studies in single center populations where more granular data on PaO2 is available than in the UNOS database have also demonstrated no impact on survival or development of BOS using donors with PaO2:FiO2<300.[20]

Size—There is accumulating evidence that undersizing allografts is associated with increased mortality and resource utilization post-transplant, particularly with undersizing below 80% recipient TLC.[21] Higher predicted total lung capacity (pTLC) ratio between pTLC donor and pTLC of recipient, which accounts for the effect of sex on lung size, is associated with improved survival up to a hazard ratio of 1.3, particularly in bilateral transplants.[22] Contrary to earlier reports in which pTLC >1.0 was not recommended for patients with emphysema, this finding held across all diagnostic groups.[23]

Graft volume reduction, including peripheral wedge resection, may also be used to improve size-matching, particularly when pTLC >1.6.[24,25] In a single center study of adult recipients, graft volume reduction was associated with a trend toward increased duration of mechanical ventilation, ICU length of stay, and overall mortality compared to size-matched recipients, but this has not been investigated in large cohorts.[21] For significantly oversized allografts, delayed chest closure, which has been associated with worse overall survival compared to all recipients but similar survival compared to matched controls, may be an acceptable strategy.[26] Lobar transplant versus use of pediatric donors remains an ongoing area of controversy for adults with small chests.[27]

Other potential sources of donor lungs

Finally, although the focus of this review is on clinically-oriented evaluations to optimize potential lung transplant donors, there are a number of structural interventions that are also essential for expanding the organ donor pool. These include allowing donor registration in community locations such as the Department of Motor Vehicles, optimization of organ and medical personnel travel logistic chains, and utilization of social networks to create positive incentives for organ donation.[28] For example, in May 2012 the social media website Facebook allowed users to specify their organ donor status along with a link to the state online donor registry. Within 24 hours online organ donation registration in the US increased between 800–12,000% depending on the state.[29]

Transplantation from non-ideal donors

There is sufficient evidence that, for any one factor that makes a donor acceptable rather than ideal, there will not be a significant negative impact on recipient prognosis. There are, however, few studies on the use of donors with multiple extended characteristics on post-transplantation outcomes. A recent single center review found increased PGD and length of ICU stay in recipients whose donors had 2 or more extended characteristics but no impact on long-term survival or BOS.[30] It is likely, however, that there is a threshold at which the accumulation of marginal factors makes the donor unacceptable.[14] Similarly, there are likely recipient factors that make transplantation from a marginal donor significantly riskier. For example, the use of extended donor criteria organs should be weighed carefully in patients with lung allocation score >70 where there appears to be increased risk of death at 1 year for extended criteria transplants.[31] Without clear evidence about specific donor-recipient combinatorial risk, development of risk assessment tools is essential.[32]

Donor management

After brain death, management strategies focus on preserving candidacy and optimizing post-transplantation lung-function. These strategies can be divided into two broad categories: donor management protocols focused on optimizing pulmonary and extra-pulmonary physiologic parameters and donor lung preservation at procurement and in transit.

Donor extra-pulmonary and physiologic management

Brain death and the preceding insults result in disruption of normal neuro-hormonal homeostatic balance. The subsequent systematic inflammatory response including hypertensive crisis from sympathetic discharge followed by neurogenic hypotension triggers an inflammatory cascade leading to disruption of the capillary-alveolar membrane. The resulting neurogenic pulmonary edema and endothelial dysfunction may lead to an inflammatory acute lung injury (ALI) similar to acute respiratory distress syndrome (ARDS). Management of the brain-dead potential donor to optimize pulmonary function therefore requires hemodynamic, neuro-endocrine, and lung specific approaches.

General management—Both before and after the catecholamine surge, the majority of brain-dead donors have some form of shock. Appropriate therapy targeting the mechanism of shock is essential (Table 2). Once euvolemia has been achieved, vasopressin is the preferred agent for maintenance of end-organ perfusion. Vasopressin appears to be particularly efficacious in brain-dead donors and has a secondary impact on reversing diabetes insipidus. The use of vasopressin increases the rate of successful organ procurement and may reduce the need for alpha-1 agonists.[33]

In addition to treating adrenal insufficiency from disruption of the hypothalamic-pituitary axis, the administration of glucorticoids may reduce inflammatory-mediated ALI and extravascular lung water accumulation.[34] The use of high dose methylprednisolone (15 mg/kg) has been associated with increased PaO2 and successful lung donation in retrospective studies, although a small randomized trial did not show a significant change in PaO2 or lung retrieval rates in donors treated with methylprednisolone versus placebo.[34] The use of thyroid replacement in potential donors remains controversial and there is no lung-specific evidence that replacement improves subsequent outcomes. Current guidelines, however, recommend either T3 or T4 intravenously in potential donors who are hemodynamically unstable.[35] Finally, there is insufficient data on the impact of donor hyperglycemia or intensive insulin management on subsequent allograft function, although most ICUs now utilize protocols targeting glucose levels below 180 mg/dl.

Lung specific management—As with ALI of other etiologies, ventilator management of the potential donor should emphasize a lower stretch (6 mL/kg predicted body weight) lung protective ventilation strategy. In a large multicenter trial, Mascia et al found that a low tidal volume, higher PEEP strategy with closed circuit suctioning and apnea testing performed without ventilator disconnection resulted in a doubling of lung procurement (27% vs 54%).[36] There was no difference in recipient 6 month survival but a trend toward decreased length of ICU stay suggesting a possible reduction in PGD. It is unknown whether

a very low tidal volume (3–5 mL/kg) approach might result in further optimization without compromising other organ transplantation because of hypercapnea.

Extrapolating from the broader literature on the importance of conservative fluid management in ARDS, maintenance of a neutral or slightly negative fluid balance with judicious crystalloids and diuretics likely improves oxygenation.[37] Similarly, bronchoscopic evaluation and removal of plugs and aspiration secretions may increase oxygenation. However, neither a conservative fluid management strategy nor routine bronchoscopy has been independently evaluated outside of a combination of strategies to optimize donor lungs.

Additional Interventions—The use of high dose nebulized albuterol or a fluid management protocol guided by non-invasive monitoring of pulse-pressure variation has not increased the number of viable lung and total organs procured, respectively.[38,39] Trials of recipient remote ischemic conditioning through thigh occlusion tourniquets are ongoing but have not shown improved PaO2 or decreased PGD in lung transplant patients.[40] Finally, the use of salvage extracorporeal membrane oxygenation (ECMO) to allow for organ donation in unstable brain dead donors remains controversial.[41]

Donor management protocols—There are multiple single center studies that have demonstrated improved rates of donor lung utilization when employing donor management protocols. In collaboration with donor ICU teams, these protocols allow for bedside support aimed at preserving and optimizing lung function through implementation of the lung management strategies discussed above. The use of these protocols has increased donor lung recovery from 20% to 40–50% compared to historical controls without an increase in PGD rates.[34,42] Moreover, the implementation of a lung-focused protocol did not impact heart, liver, kidney, or pancreas retrieval rates or long-term kidney graft survival in a recent multicenter study.[43]

Lung preservation at procurement and in transit

Routine preservation—Most institutions use a similar approach to preservation of donor lungs, with some minor variations regarding preservation solution and flushing, storage temperature, and lung ventilation. It is standard practice to perform anterograde flushing via the main pulmonary artery with 60 mL/kg of a hypothermic solution, typically low-potassium dextran.[44] Most centers add prostaglandin E1 to the flush solution as an anti-inflammatory agent and to limit hypothermia-induced vasoconstriction. Similarly heparin is commonly administered to prevent thrombus formation. Retrograde flushing via the pulmonary veins may improve clearance of fat and pulmonary emboli that enter the bronchopulmonary circulation. Although supported by data in animal models, single center non-randomized trials have not shown an impact on PGD and one study found a trend toward increased fatal anastomotic dehiscence with retrograde flushing.[45]

Data in animal models supports partial lung inflation to 50% TLC with 30–50% FiO2 to prevent ischemic damage during transport, although this has not been studied clinically.[46] Finally, goal temperatures during transportation are 4–8 degrees Celsius, commonly through storage with preservation fluid surrounded by multiple layers of plastic bags all placed on ice. The actual organ temperature maintained with this approach is unclear.

Ex vivo perfusion reconditioning and preservation—Despite peri-operative optimization, the organ remains vulnerable to injury in the post-procurement period, particularly for prolonged ischemic time above 6–8 hours. Lung tissue damage, manifested as PGD, remains a significant cause of mortality in the initial post-operative period and for subsequent morbidity. Ex-vivo lung perfusion (EVLP) allows for normothermic perfusion and ventilation of organs prior to transplantation. EVLP protocols differ by the use of a cellular (red blood cells with target hematocrit of 14–20%) or acellular perfusate, target flow/cardiac output and pulmonary arterial pressure, target temperature (32 vs 34 degrees Celsius), tidal volume (5–7 mg/kg ideal body weight), FiO2 (12–50%), and whether the left atrium is closed to prevent collapse of the pulmonary veins. [47] Approaches also differ with regard to timing of EVLP initiation (in donor hospital versus in recipient hospital after a period of cold preservation) and duration of EVLP. To date, there are no direct comparisons of EVLP protocols in humans although animal research is ongoing.

Regardless of the protocol, EVLP has been best studied as a “rescue” therapy for organs—from donation after cardiac death (DCD) or brain dead donors whose PaO2 and function fall below acceptable criteria for transplant—that might otherwise be rejected. Based on the experience from the University of Toronto, donor lungs are acceptable following EVLP if they have a PaO2:FiO2 >400 and pulmonary artery pressures, airway pressures, and pulmonary compliance that remains stable (defined as <15% worsening) or improved.[47] The role of serial radiographic and bronchoscopic assessment in addition to these physiologic parameters remains unclear. There is, however, growing interest in sampling EVLP perfusate for novel biomarkers to assess transplantability.[48]

Centers utilizing EVLP have had a 15–33% increase in transplantation volume suggesting that this is an effective approach to expanding the donor pool.[49] In the largest experience, Cypel et al reported decreased rates of grade 3 PGD despite lower PaO2 in EVLP donors.[50] Several case control studies have found similar lengths of hospitalization and rates of acute and chronic rejection in patients transplanted with marginal donor lungs conditioned via EVLP.[51,52] A large multicenter trial in the UK, however, found higher rates of grade 3 PGD, need for post-transplant ECMO, significantly increased cost, and almost double the one year mortality for patients who received EVLP lungs.[53] Although the authors caution drawing conclusions given the small number of patients involved (18 in the EVLP arm) and a change in the EVLP protocol midway through the trial, these findings suggest that further standardization of EVLP techniques may be necessary to allow effective, wide-spread adoption of this technology.

In addition to optimizing lung function from DCD donors and marginal organs from brain dead donors, there is ongoing interest in normothermic EVLP instead of hypothermic preservation for standard-criteria lungs. For example, the INSPIRE trial is an international, multicenter randomized control trial of a portable normothermic perfusion devise compared to standard cold storage.[54]

Finally, there are a number of studies focused on the addition of pharmacologic agents to the EVLP circuit as a mechanism of improving transplantability and short and long-term allograft function. These include inhaled agents such as carbon monoxide, nitric oxide, and

surfactant; the addition of antibiotics such as azithromycin; adenoviral gene vector therapy targeting inflammatory pathways; other anti-inflammatories such as N-acetylcysteine; and the injection of human mesenchymal stem cells to improve pulmonary edema.[55] Ongoing research is also examining the impact of EVLP on removal of donor antigen presenting cells and on the post-transplantation pulmonary microbiome.

Conclusions

Continued expansion of the lung transplantation donor pool requires utilization of novel organ donor registration strategies, commitment to an expanded socio-demographic and clinical definition of ideal donors, protocolized physiologic management of organ donors in the ICU, and utilization of ex vivo approaches to preserve and recondition donor lung prior to transplantation.

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KEY POINTS

- Donor evaluation is best conceptualized as weighing a constellation of specific patient and organ-related risk factors and their impact on post-transplantation allograft function.
- There is sufficient evidence that, for any one factor that makes a donor acceptable rather than ideal, there will not be a significant negative impact on recipient prognosis.
- Following brain death, donor management should focus on protocol-driven optimization of pulmonary and extra-pulmonary physiologic parameters.
- Ex vivo lung perfusion is a viable intervention to recondition lungs that would otherwise fall below acceptable criteria for transplant.

Table 1

Ideal versus acceptable donor criteria

Ideal	Acceptable	Additional data needed
Donor characteristics		
Age < 55	• Age > 65	• Age > 70
Less than 20 pack year smoking history	• Less than 40 pack years and no active smoking • Less than 20 pack years and actively smoking	• Greater than 40 pack years
No significant medical history	• Hepatitis B, if access to prophylactic lamuvidine • Donor diabetes for planned bilateral lung transplant • Low transmission risk malignancy (early stage basal cell, cervical carcinoma in situ, localized low-grade (Gleason score ≤6) prostate cancer)	• Hepatitis C, if access to direct-acting antiviral drugs • Donor diabetes for planned single lung transplant • Early stage melanoma, breast, ovarian, and colonic cancer with a significant cancer free period following curative surgery
Organ characteristics		
No evidence of active pulmonary infection or organisms on sputum gram stain	• No active infection with a multi-drug resistance organism for which appropriate post-transplant antibiotics or antifungals cannot be implemented	• Transplantation from donors with CRE or ESBL organisms; recent influenza or other viral infections
PaO2 >300 mmHg on 100% FiO2 and PEEP 5	• PaO2 >200 mmHg on 100% FiO2 and PEEP 5	• PaO2 <200 mmHg on 100% FiO2 and PEEP 5
Appropriate size matching	• pTLC at least >0.8 and ideally between 0.90-1.3, particularly for bilateral transplants	• Optimal pTLC for recipients with emphysema • Use of graft volume reduction and/or delayed chest closure for significantly oversized (pTLC >1.6) patients

CRE=carbapenem-resistant enterobacteriaceae; ESBL=extended-spectrum beta-lactamases; FiO2=fraction of inspired oxygen; mmHg=millimeters of mercury; PaO2=partial pressure of arterial oxygen; pTLC=predicted total lung capacity

Table 2

Approach to General Donor Management

Hemodynamics	
Hypovolemic shock	• Crystalloid repletion to achieve euvolemia • Consider albumin 5% for fluid resuscitation • Avoid hydroxyethyl starch fluid resuscitation • Consider red blood cell transfusion for hemoglobin <7 g/dL
Vasodilatory shock	• Goal central venous pressure 6–8 mmHg • Goal mean arterial pressure >60 mm Hg • Vasopressin 0.01–0.04 IU/min to maintain hemodynamic goals • Consider addition of dopamine, norepinephrine and epinephrine in refractory shock
Cardiac shock	• Consider placement of pulmonary artery catheter to tailor therapy • Dopamine to optimize central venous pressure, mean arterial pressure, and, when available, mixed venous oxygen saturation • Consider addition of norepinephrine and epinephrine in refractory cardiogenic shock despite dopamine and vasopressin
Hormonal	
Diabetes insipidus	• Vasopressin 0.01–0.04 IU/min, consider higher doses with caution • Desmopressin if persistent ongoing diabetes insipidus with sodium >145–150 mmol/L, titrated to serum sodium, urine output, and urine osmolarity
Adrenal insufficiency	• Intravenous methylprednisolone 15 mg/kg, consider subsequent infusion at 100 mg/hr
Thyroid deficiency	• Consider intravenous T3 (4 μg bolus then 3 μg/hr) or T4 (20 μg bolus then 10 μg/hr) in unstable donor despite hemodynamic optimization
Hyperglycemia	• Consider standard intensive care unit management protocol targeting glucose <180 dg/mL