Review Article

Lung donor selection criteria

John Chaney[1], Yoshikazu Suzuki[2], Edward Cantu III[2], Victor van Berkel[1]

[1]Department of Cardiothoracic Surgery, University of Louisville School of Medicine, Louisville, KY, USA; [2]Department of Surgery, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Correspondence to: Victor van Berkel, MD, PhD. Department of Cardiothoracic Surgery, University of Louisville School of Medicine, 201 Abraham Flexner Way, Suite 1200, Louisville, KY 40202, USA. Email: victor.vanberkel@louisville.edu.

Abstract: The criteria that define acceptable physiologic and social parameters for lung donation have remained constant since their empiric determination in the 1980s. These criteria include a donor age between 25-40, a arterial partial pressure of oxygen (PaO_2)/FiO_2 ratio greater than 350, no smoking history, a clear chest X-ray, clean bronchoscopy, and a minimal ischemic time. Due to the paucity of organ donors, and the increasing number of patients requiring lung transplant, finding a donor that meets all of these criteria is quite rare. As such, many transplants have been performed where the donor does not meet these stringent criteria. Over the last decade, numerous reports have been published examining the effects of individual acceptance criteria on lung transplant survival and graft function. These studies suggest that there is little impact of the historical criteria on either short or long term outcomes. For age, donors should be within 18 to 64 years old. Gender may relay benefit to all female recipients especially in male to female transplants, although results are mixed in these studies. Race matched donor/recipients have improved outcomes and African American donors convey worse prognosis. Smoking donors may decrease recipient survival post transplant, but provide a life saving opportunity for recipients that may otherwise remain on the transplant waiting list. No specific gram stain or bronchoscopic findings are reflected in recipient outcomes. Chest radiographs are a poor indicator of lung donor function and should not adversely affect organ usage aside for concerns over malignancy. Ischemic time greater than six hours has no documented adverse effects on recipient mortality and should not limit donor retrieval distances. Brain dead donors and deceased donors have equivalent prognosis. Initial PaO_2/FiO_2 ratios less than 300 should not dissuade donor organ usage, although recruitment techniques should be implemented with intent to transplant.

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Introduction

Lung transplantation is an established therapy for selected patients with end-stage pulmonary disease. Since the first successful lung transplant in 1983 by Dr. Joel Cooper and his team, over 42,000 recipients have benefitted from this procedure worldwide. Advances in surgical techniques, postoperative care, and immunosuppression therapy have led to improved short- and long-term survival following lung transplantation. Despite this success, the number of suitable lung donors remains a significant limitation. Today many donors are judged based on empiric criteria developed in the 1980s (See *Table 1*) (2,3).

Most centers agree that these criteria are too strict and use extended criteria donors (ECD) that do not completely meet the traditional empiric criteria (4). Many centers advocate use of ECD to effectively increase the donor pool with similar transplant outcomes (2,5-10). There is considerable variation in practice patterns among these centers and no uniformly accepted discriminating metric (6).

In-hospital mortality for lung transplantation is higher than for other solid organs. A significant contributor to this early hazard is primary graft dysfunction (PGD) (11). PGD occurs in up to 25% of recipients with associated 30 days

Table 1 Ideal lung donor criteria (1)	
Age	20-45
PaO_2:FiO_2	>350
Smoking history	None
Chest X-ray	Clear
Ventilation days	<5
Microbiology	Gram stain negative
Bronchoscopy	Clear
Ischemic time	<4 hours

mortality of 40-50%; compared to 5-10% without PGD (12). Accumulating evidence suggests that PGD is the end result of a series of injuries occurring in the donor lung from the time of brain death to reperfusion in the recipient (13). Therefore, concern over PGD may drive concern over lung donors, and thus limit the number of organs considered usable for transplant. Given the increasing burden of lung disease, the extremely limited number of suitable lung donors, and increasing waitlist mortality, it is not surprising that an increasing numbers of ECDs are being used. In the era of the lung allocation score, with preferential allocation to sicker recipients, it becomes more important to understand not only which ideal criteria can be ignored, but also in which context. Here, we break down donor criteria by individual factors and examine their effect on outcomes.

Age

Over the last 30 years, the average age of donors accepted for transplant has steadily increased. Retrospective cohort analysis of OPTN data revealed no increases in one year graft failure with donors aged 18-64. Ages <18 and >64 were associated with increased failure rates at one year but were not associated with increased PGD (14). Retrospective review of UNOS data from 2000-2010 confirms an increase in 1- and 3-year mortality for donors over the age of 65 without increases in bronchiolitis obliterans syndrome (BOS) (15). Further stratification into age groups [50-54, 55-59 and 60-64] did not reveal differences in one year mortality or FEV_1 (16). Available literature favors consistent outcomes for donors within the range of 18-64 years.

Gender

Donor and recipient gender combinations have been analyzed with mixed results. Fessart *et al.* failed to discern a difference in recipient survival after analysis of all gender combinations (17). Another single center retrospective study demonstrated an increase in survival and decrease in BOS for donor recipient gender mismatches (M→F and F→M). Male donor to male recipients specifically had a significant decrease in survival (18). International Society of Heart and Lung Transplant (ISHLT) registry review from 1995-2002 reflected a decreased survival in female donors to male recipients. Female donor to female recipient demonstrated a short and long term survival benefit (19). These results coincided with a multicenter study in France (20). The exact gender interactions between donor and recipient have yet to be defined to accurately shape our practice of transplant selection. There are questionable effects of hormones and size mismatch that have yet to be delineated in the literature.

Race

Retrospective review of lung transplants from 1997 to 2007 of race matched donors and recipients conferred a 3.3% decreased risk adjusted mortality at five years and 12% overall mortality in recipients with cystic fibrosis (CF), idiopathic pulmonary fibrosis (IPF) and single lung transplant (SLT). No changes in one year rejection rates were associated with race matching. Donor African American lungs reflected an increased risk of death regardless of recipient. Overall, specific recipient race was not associated with survival variability (21).

Smoking history

In the UK, a smoking history in donor lungs is associated with decreased recipient survival as compared to non-smoker donor lungs. The recipient survival, however, remains greater than that of the wait list population (22). This raises the argument that patients with high mortality risk would benefit from transplantation rather than succumb to illness on the waiting list. The interpretation of this data is also limited given recipients of smoker lungs were riskier candidates prior to surgery. Smoker donor lungs confer a higher risk of grade 3 PGD (23). A retrospective review of UNOS data on 766 heavy smoker donor lungs (>20 pack year history) revealed no increases in BOS or median survival (24). An additional single retrospective study of smoking donors revealed a worse early survival but no effect on long term survival and BOS incidence (25). This was confirmed by an additional retrospective single institution study that had

prolonged postoperative intubation and ICU stay in smokers but equivalent survival at three years (26). The overall findings coincide with an initial higher postoperative risk, and equivalent to higher long term recipient mortality risk, for smoker donor lungs as compared to non-smoker donor lungs. The mortality of patients receiving smoker donor lungs does reflect a lower mortality risk than that of patients on the transplant waiting list.

Bronchoscopic findings and cultures

Post transplantation pneumonia and sepsis are serious concerns to the transplant surgeon and previous guidelines for chest X-ray and bronchoscopy attempt to avoid transmission to immunosuppressed recipients. Gram stain evaluation of airways in a single center retrospective study found 12% of donors with a positive gram stain subsequently developed recipient pneumonia while 20% of negative gram stain donors went on to develop pneumonia. This refutes the association of donor gram stain with recipient pneumonia. In this study, however, donor lungs were not accepted if there was evidence of frank aspiration on bronchoscopy (27). Prospective analysis of donor airway cultures and bronchial tissue cultures revealed a <1.5% transmission rate of donor organ contamination (28). The lack of infection transmission from donor to non-suppurative based recipients is also been confirmed by two separate studies (29,30). With appropriate antibiotic prophylaxis to cover Pseudomonas and Staph aureus, risk of transmission of donor associated infection is negligible.

Radiographic findings

Donors undergo multiple radiographs prior to surgery. The high degree of interpretation variability have diminished the role in donor selection criteria (31). One third of possible donor radiographs in a retrospective survey had infiltrates, of which greater than half improved or spontaneously resolved. Improvement in infiltrates did not impact transplantation rates and led to unnecessary rejection. All patients transplanted in this study with positive infiltrates were alive at one year follow-up (32). No studies were found that correlated chest radiograph findings to recipient infections. The literature on radiographic donor exclusion is extremely limited, and the topic warrants further investigation.

Size mismatch

A recent review by Barnard published in 2013 thoroughly outlines size criteria for donor/recipient, and their results are briefly summarized here (33). Total lung capacity (TLC), recipient pathology (obstructive *vs.* restrictive), and height all factor in to appropriate matches. For double lung transplants, patients with emphysema should be matched to a donor with a 67-100% of the recipient's TLC. No definitive data is available for SLT for emphysema. For pulmonary hypertension and CF patients, the predicted total lung capacity (pTLC) of the donor may safely reach 120% of the recipient actual TLC. Due to the limitations in TLC that occur in pulmonary fibrosis, the recommendation for donors pTLC is to be within 20% of the halfway point between the recipients actual TLC and pTLC. For SLT for fibrotics, the donor pTLC should be within 20% of the recipient's pTLC. Little data exists for transplantation in overt size mismatch, but some suggest it is preferable to slightly oversize if possible and not undersize less than 80% (34).

Ischemic time and donor distance

Retrospective review of UNOS data of 6,055 transplants revealed no increased incidence of BOS or three years mortality in recipients with local, regional or national lung donors despite national ischemic times of (342±90) minutes (35). Additional single center studies verify no change in survival for ischemia greater than six hours (36-40). Donor ischemia time >7 hours and donor age >50 years compounded, however, was associated with decreased recipient survival at two years (41).

Donation after cardiac death

After evaluating the literature for effects of ischemia on recipient outcomes, the question of donation after cardiac death (DCD) use as opposed to beating heart brain dead donors inevitably follows. The largest single center study with 409 DCD lungs revealed a decrease in graft survival that did not reach statistical significance. The patient survival and BOS were comparable (42). Smaller, single center studies reveal either similar survival rates (43,44), or a modest decrement in survival (45). A single institutional study out of Madrid revealed PGD in 72%, Survival rates of 51% at five years, and BOS of 45% at five years (46). Use

of DCD donor lungs revealed a 100% survival at almost a year in eight patients (47). In total, these studies suggest the benefit of using DCD donors as a means to expand the available donor pool.

High risk donors

The Centers for Disease Control and Prevention (CDC) label high risk donors as those with exposure to HIV, prison inmates, IV drug users, prostitution history, high risk sexual history, and hemophiliacs. Limited data is available for lung transplantation in CDC high risk donors. Review of UNOS database on CDC high risk donors demonstrated equivalent one year mortality, postoperative infection, stroke and dialysis with normal donors. Around 9% of lung donors were classified as high risk and risk of disease transmission was less than 1%. Interestingly 95% of recipients surveyed would accept an organ from a high risk donor with an expected donor pool expansion of 10% (48).

Oxygenation

Arterial partial pressure of oxygen (PaO_2) is a traditional way to measure lung function. Donors with initial PaO_2/FiO_2 of <300, that improved to >300 with recruitment maneuvers, used in Australia were not associated with a decreased 30 days, 1, 2, 3 yrs survival or recipient PaO_2/FiO_2 ratio (8). High dose steroid administration after brain death was associated with an increase in PaO_2/FiO_2 of 16 +/-14 and a decrease of 34.2 +/-14 if steroids were not given. The outcome of recipients receiving steroid treated donor lungs was not analyzed in this study (49). Most importantly, UNOS data from 2000 to 2009 of 12,045 transplants failed to demonstrate a PaO_2 association with decreased survival, even with a PaO_2 of less than 200 in 1,830 patients (50). This may be due to preoperative gasses that are lower on initial reported PaO_2 and significantly improve after recruitment maneuvers, which are not consistently captured in the database.

Ex vivo lung perfusion (EVLP)

EVLP is an emerging technique used to evaluate and potentially salvage high-risk donor organs typically not suitable for lung transplantation (51). Steen initially utilized this technique to evaluate a DCD donor (52) and their success has sparked several studies around the world (51,53-57). These studies have demonstrated similar length of mechanical ventilation, rate of PGD, length of stay and mortality. How this technology will be implemented in allocation has yet to be determined despite the considerable promise they imply. Despite these challenges, it appears that the future of lung transplantation will capitalize on EVLP to safely expand the donor pool by expanding the limits of what defines a suitable donor.

Conclusions

There is little data to suggest that any of the historical criteria for defining the ideal lung transplant donor impact either short or long term outcomes. For age, donors should be within 18 to 64 years old. Gender may relay benefit to all female recipients especially in male to female transplants. Negative outcomes are associated with female donors to male recipients. Race matched donor/recipients have improved outcomes and African American donors convey worse prognosis. Smoking donors may decrease recipient survival post transplant, but provide a life saving opportunity for recipients that may otherwise remain on the transplant waiting list. No specific gram stain or bronchoscopic findings are reflected in recipient outcomes. Chest radiographs are a poor indicator of lung donor function and should not adversely affect organ usage aside for concerns over malignancy. Ischemic time greater than six hours has no documented adverse effects on recipient mortality and should not limit donor retrieval distances. Brain dead donors and deceased donors have equivalent prognosis. Initial PaO_2/FiO_2 ratios less than 300 should not dissuade donor organ usage, although recruitment techniques should be implemented with intent to transplant.

Although there have been multiple trials on individual lung donor criteria that fail to show negative recipient prognosis (58), there are few studies that evaluate the effects of multiple extended criteria compounded together in one donor lung. These compromises in physiology may have untold effects on PGD and overall patient mortality. In additional to donor selection, it is imperative to consider the recipient's pathology as a major harbinger of overall transplantation outcome (59). It is currently our recommendation that any single criteria outside of the historical ideals can safely be ignored, but we caution that the cumulative effects of multiple extended donation criteria in one donor have not been studied.

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