A Review of Lung Transplant Donor Acceptability Criteria

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(A consensus report from The Pulmonary Council of the International Society for Heart and Lung Transplantation)

There is a paucity of literature regarding acceptability criteria for human lung donors. Most of the currently available data are based on small, center-specific reports from the early days of lung transplantation that have not been substantiated in prospective, controlled trials or even large, uncontrolled trials. Despite the great need for suitable lung donors, only a minority of potential multiorgan donors are utilized for lung donation (Figure 1). With the mortality while waiting for transplantation increasing on a yearly basis, and the ever-increasing number of patients waiting for donor lungs (Figure 2), there is now a desperate need to expand the pool of useable donor organs for transplantation. Several small, center-specific reports have documented the efficacious use of "marginal" or less-than-optimal donor organs for this purpose, with outcomes not unlike the those from studies utilizing "optimal donors" (Table I). Other investigators have noted the importance of ultimately defining the limits of extended donor utilization.[1] The purpose of this report is to identify the evidence, or lack thereof, supporting the current recommendations for donor lung acceptability. In this regard a number of parameters are reviewed. These include donor age, gender, cause of death, length of time on mechanical ventilation, arterial blood gas levels, radiographic changes, sputum gram-stain findings, ABO incompatibility, organ-size matching, graft ischemic time and other donor co-morbid conditions such as history of smoking, asthma and cancer.

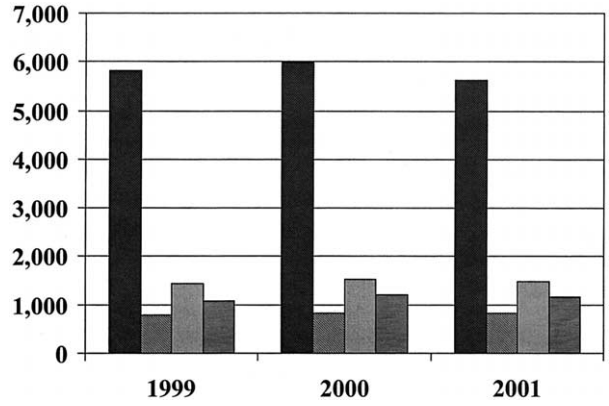

FIGURE 1 Cadaveric donors offered (≥ 1 organ) and lungs recovered and transplanted, January 1999 to November 2001. Filled bars: donors offered; diagonally lined bars: lung donors; vertically lined bars: lungs recovered; horizontally lined bars: lungs transplanted. (data source: UNOS/OPTN, as of March 29, 2002).

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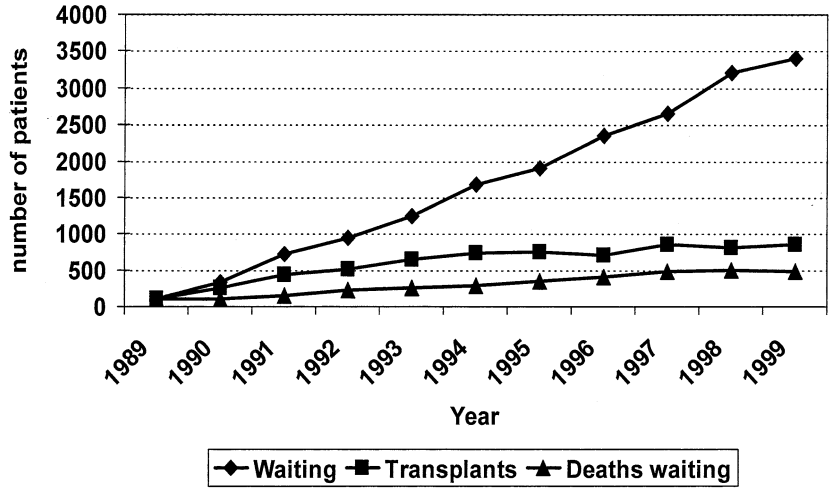

FIGURE 2 Yearly increase in the number of patients waiting, lung transplants performed and deaths while on the waiting list. (From Trulock, *Semin Resp Crit Care Med,* 2001 [UNOS data] with permission).

DONOR AGE

Background

Generally accepted donor criteria include donor age <55 years.[2-4] However, several recently published reports have shown that older donor lungs can be transplanted successfully. Older donor age might theoretically have beneficial as well as detrimental effects on overall outcome. These effects are attributable to the age and the lung tissue or the donor's aging immune system. Older lungs may have increased susceptibility to certain cancers and infection, and sub-clinical emphysematous changes with reduced lung function may be present. With declining immune function in older lungs, they may be less prone to rejection. A considerable number of mononuclear cells are present in the human donor lung, adhering to the vascular endothelium and in the interstitial space.[5] These cells include monocytes/macrophages as well as lymphocytes and natural killer (NK) cells. These cells may mediate allostimulation and graft-versus-host effects, but also may have beneficial tolerogenic effects. Age-dependent alterations of immune function involve both the innate and adaptive parts of the immune system. In older individuals, dendritic cells have reduced functional capacity to stimulate immune responses.[6] On the other hand, advanced age is associated with augmented innate immune responses such as enhanced CD14–NOS2 signaling in response to cytokines.[7] With regard to the adaptive immune system replicative senescence due to thymic involution has been described.[8] From these data, the effect of older donor lungs on outcome after lung transplantation cannot be predicted directly, and probably depends on the net effect of the functional properties of these lungs together with the individual responses of the recipient.

TABLE I Currently accepted "ideal" donor

- Age <55 years
- ABO compatibility
- Clear chest radiograph
- PaO_2 >300 on FIO_2 = 1.0, PEEP 5 cm H_2O
- Tobacco history <20 pack-years
- Absence of chest trauma
- No evidence of aspiration/sepsis
- No prior cardiopulmonary surgery
- Sputum gram stain—absence of organisms
- Absence of purulent secretions at bronchoscopy

From ref. 12 with permission.

In situations in which the allocation system allows lung allocation to a specific center and not to a specific patient, attempts are often made to match the age of the donor with the age of the recipient; for instance, the organ of an older donor will be transplanted into an older recipient and not into a young cystic fibrosis patient. However, no evidence exists to support or refute the use of this practice.

Clinical Studies

Novick and colleagues[9] evaluated all lung transplantations performed between 1987 and 1997 that were reported to the International Society for Heart and Lung Transplantation (ISHLT) with regard to donor age. They found that donor age of <10 years or

TABLE II Summary of literature for the use of older lung donors

Reference	*n*	Design	Outcome
Novick et al (1999) (ref. 9)	284/5,052	Retrospective	Decreased survival
Meyer et al (2000) (ref. 10)	23/1,800	Retrospective	No adverse affect on intermediate survival
Bhorade et al (2000) (ref. 12)	9/52	Retrospective	No adverse affect on ventilator time, hospital stay or hospital survival
Hosenpud et al (2001) (ref. 14)	*15,465	Retrospective	Risk factor for 1- and 5-year mortality (quadratric)

*Numerator not defined.

> 50 years may be associated with a slight increase in 1-month and 1-year mortality. However, on multivariate analysis, donor age was not an independent predictor of early survival except when quadratic terms of this variable were analyzed. In contrast, there was a negative interaction between donor age and extended graft ischemic time, particularly when donor age was > 55 years and ischemic time was > 6 hours.

A cohort of 1,800 lung transplant recipients transplanted between 1993 and 1996 and reported in the ISHLT registry, with a follow-up of ≥ 2 years, was also analyzed.[10] Again, the combination of donor age > 55 years and ischemic time of > 7 hours led to a reduced intermediate (2-year) survival.

Sommers and colleagues[11] analyzed factors influencing outcomes in 27 pairs of single-lung recipients from the same donors. In this scenario, donor age was found to influence the alveolar–arterial oxygen gradient immediately post-transplant in a multivariate logistic regression analysis.

In a single-center study on liberalization of the donor pool, Bhorade and colleagues[12] found that an increase in the use of donors aged > 55 years did not impact negatively on length of time for intubation, hospital stay or hospital survival in 9 cases. In another study, Sundaresan et al.[13] extended their donor pool and, among other parameter extensions, used 2 donors > 55 years. Outcomes among recipients of these allografts were similar to those from "acceptable" donors.

In the latest data set of the ISHLT registry, including data of 15,465 lung and heart–lung transplantations,[14] donor age (quadratic) was identified as a risk factor for 1- and 5-year mortality ($p = 0.002$ and $p = 0.01$, respectively). This effect was even stronger when the interaction between donor age and ischemic time was examined. With a donor age of 60 years, the odds ratios were 1.12, 1.55 or 2.14 if ischemic time was 1, 4 or 7 hours, respectively. Similarly, an interaction between donor age and the center's volume of transplants was found. With a donor age of 60 years, the odds ratios were 0.57, 1.16 or 2.37 in centers performing 55, 30 or 5 transplants per year, respectively.

In summary, although smaller studies have not shown a survival disadvantage with the use of older donors, larger registry studies have shown a negative affect on intermediate- and long-term survival, particularly when combined with increased graft ischemic time (Table II). This potentially reflects the concept of diminished "functional reserve" in older donor organs, in whom the effects of other adverse factors (such as long ischemic time or low center volume) are additive or magnified.

ARTERIAL BLOOD GASES

The origin of the "standard" arterial blood gas criteria for evaluating the suitability of the potential pulmonary donor is shrouded in the mists of time. In 1987 Harjula et al[15] described a single case of peri-operative graft failure in which the arterial partial pressure of oxygen (PaO_2) was < 100 mm Hg, with a fraction of inspired oxygen (FIO_2) of 0.4 (i.e., PaO_2/FiO_2 ratio <250), and it is likely the acceptability ratio of 300 (PaO_2 of 120 mm Hg on an FiO_2 of 0.4) was then arbitrarily chosen to provide a slight margin of safety. It is more puzzling as to why this standard has been so closely adhered to since that report. The literature provides no answers as no studies have addressed this issue specifically.

Nevertheless, consideration of the alveolar–arterial (A-a) gradient underpins any rational discussion of arterial blood gases. Assuming normal lung structure and function (i.e., normal ventilation–perfusion matching), at sea level with water vapor pressure of 47 mm Hg, with a respiratory exchange ratio of 0.8 and an adequate minute ventilation, an FIO_2 of 1.0 should produce a PaO_2 of: $1.0 \times (760 - 47) - 1.25 \times PaCO_2$ (assume 40 mm Hg) = 663 mm Hg. Experience indicates that few donors have a PaO_2/FIO_2 ratio of >600 and, importantly, as described by

TABLE III Summary of literature for donor blood gases (PaO_2/FIO_2 <300)

Reference	*n*	Study design	Outcome
Harjula et al (1987) (ref. 15)	1	Case report	Primary graft failure
Shumway et al (1994) (ref. 23)	25 (1)	Case series	No adverse affect
Sundaresan et al (1995) (ref. 13)	6	Retrospective review	No adverse affect

Gabbay et al,[16] it is the final pre-operative measurement of gas exchange that is relevant. Donor gas exchange has been shown to be sensitive to small changes in filling pressures with a central venous pressure (CVP) of 8 to 12 cm H_2O associated with an increased A-a gradient.[17] Other potential causes of deterioration in gas exchange include neurogenic pulmonary edema, donor-derived fat[18] or cerebral[19,20] pulmonary emboli as well as thromboembolism.[21] In 1998, Follette et al.[22] in a non-blinded retrospective review, showed that managing potential lung donors with high-dose steroids led to a significant improvement in PaO_2/FIO_2 ratio of 16 ± 14 ($p < 0.01$), whereas a decrease of 32.4 ± 14 ($p < 0.003$) was seen in donors not treated with steroids. Outcomes after lung transplantation were not provided. In Gabbay's series, active management of the potential pulmonary donor was able to salvage lungs for transplant in 20 of 59 donors with an initial PaO_2/FIO_2 of <300, with no demonstrable effect on duration of stay in intensive care unit (ICU), perioperative survival (95%) or 3-year survival (62%) when compared with outcomes achieved with "ideal donors." Notably, in all cases, the final donor PaO_2/FIO_2 ratio was >300.

The broad case of use of the marginal donor (defined as any criterion outside the ideal) has been examined in a number of small retrospective analyses, 4 of which have provided data on arterial blood gases. The first, by Shumway et al[23] in 1994, described an aggressive but practical approach to solving the donor availability crisis. The criterion for acceptable arterial blood gases was still a PaO_2/FIO_2 ratio of >250. Actuarial survival in 25 recipients (to 18 months) was not affected adversely by these liberal criteria. Unfortunately, individual gas exchange data were provided for only 3 cases, of which 2 had "ideal" gases and 1 a PaO_2/FIO_2 of >250. In 1995, Sundaresan et al[13] described 6 of 44 marginal donors with a PaO_2/FIO_2 <300. Although individual data were not presented, these 6 recipients paradoxically had a lower (not significantly) A-a gradient of ~210 mm Hg (from the graph) vs 304 mm Hg (reported) for "ideal" recipients, in the immediate post-operative period. Overall, the recipients of marginal donors had ventilator time, post-operative oxygenation and survival data that were similar to the ideal donor group. In 2000, Bhorade et al.[12] described outcomes achieved in 52 recipients of "extended" donors. Short-term (operating room and ICU complications) and longer-term outcomes (1-year lung function and survival) were not significantly different. All donors had a PaO_2/FIO_2 ratio of >350, however. Strategies to manage the special case of unilateral donor pulmonary dysfunction were described by Puskas et al[24] in 1992. In 4 donors with unilateral abnormalities on chest X-ray or on bronchoscopic examination of the tracheobronchial tree, the PaO_2/FIO_2 ratio improved from 246 ± 47 to 499 ± 43 ($p < 0.004$) once single-lung ventilation and perfusion were established intraoperatively. Finally, direct pulmonary vein blood gas sampling may also have utility in assessing the adequacy of gas exchange in the setting of unilateral abnormalities.[25]

In summary, there is inadequate data regarding the risk/benefit ratio for the lower limit of acceptability for donor arterial blood gases (Table III).

CHEST X-RAY FINDINGS

Traditional donor requirements[26] include a "clear" chest X-ray (CXR), even though it is well recognized that plain radiology may underestimate structural abnormalities.

Typically, donor CXR reflects the state of hydration, degree of neurogenic pulmonary edema, presence of pulmonary contusion or sepsis and gross antemortem pathologic results. The literature on radiologic features is even less precise than the descriptions of gas exchange because it relies to a greater degree on subjective impression and individual determination. Simply put, the sensitivity and specificity of any finding depends to a large degree on the observer. Interobserver variability is not inconsiderable, especially given that donor CXRs are often reported by non-radiologists.

Again, there is a paucity of data for establishment of firm guidelines regarding CXR findings. Gabbay et al[16] found that 39 of 64 marginal donors showed evidence of pulmonary edema ($n = 9$), hydropneumothorax ($n = 11$) or collapse/consolidation/pleural

TABLE IV Summary of literature for abnormal donor chest X-ray

Reference	*n*	Design	Outcome (survival)
Gabbay et al (1999) (ref. 16)	39/64	Retrospective review	No adverse affect
Sundaresan et al (1995) (ref. 13)	39/44	Retrospective review	No adverse affect
Bhorade et al (2000) (ref. 12)	5/52	Retrospective review	No adverse affect

effusion ($n = 21$), but these findings did not mitigate success. Importantly, 12 of 101 "ideal" donors developed radiologic features of pulmonary edema or sepsis that prevented organ procurement. Other investigators have provided less detailed descriptions of CXR changes, such as Shumway et al.,[23] who indicated that minor CXR infiltrates were acceptable. Sundaresan et al,[13] had 39 of 44 marginal donors with abnormal CXRs without a perioperative death, but the specific outcomes of individual CXR findings were not presented. In an overview study from this group, Meyers et al[27] reported in 1999 that 1 and 5-year survival rates for recipients of marginal donors ($n = 118$) were 85% and 51%, respectively, compared with 81% and 53% for recipients of ideal donors ($n = 332$). Pierre et al[1] reported that unilateral pulmonary infiltrates are considered acceptable, but that bilateral diffuse infiltrates are associated with adverse graft function. Bhorade et al[12] described satisfactory outcomes in 5 of 61 recipients of "extended" donors who had minor atelectasis on CXR. Importantly, none had abnormal findings at bronchoscopy. As mentioned earlier, Puskas et al[24] defined a practical strategy for assessing the potential use of the contralateral lung of a donor pair where there is unilateral lung dysfunction or unilateral radiologic change.

In summary, there are no adequate data to provide firm guidelines regarding utilization of donors with abnormal CXRs (Table IV).

BACTERIAL COLONIZATION AND INFECTION

Background

Historically, donor lung infection has always been considered an absolute contraindication for lung transplantation.[28-31] This is one of the reasons why many potential multiorgan donors will not become actual lung donors.[32] The brain-dead donor is at risk for airway aspiration. Endotracheal intubation and mechanical ventilation of the donor after brain insult is a necessary standard practice. Length of intubation is associated with colonization of the tracheobronchial tree and predisposes to ventilation-acquired pneumonia by eliminating the upper-airway protective mechanisms.[32] Intubation for > 3 days therefore has been considered by some to be a relative contraindication. In addition, grossly purulent secretions on bronchoscopy or a sputum gram stain with many white blood cells (>15 neutrophils per high-power field [×400]) or fungi has often ruled out lung donation.

In a study by the Leuven Lung Transplant Group conducted between 1991 and 1992, 116 of 141 multiorgan donors (82.3%) were dismissed as potential lung donors. The lungs were turned down because of purulent secretions or evidence of aspiration in 20 patients (17.2%) and because of prolonged ventilation in another 11 patients (9.5%).[34]

Assessment of the Donor Lung

Bronchoscopy is advocated as a screening measure in multiorgan donors to select potential lung donors. This test is a prerequisite for most transplant teams to accept a donor lung offer especially when aspiration of gastric content and/or infection is suspected. The presence of gross inflammation or purulence usually precludes use of the lungs. Riou et al[35] reported that only 33% of all brain-dead donors and 62% of ideal donors, based on CXR and arterial blood gas analysis, had normal fiber-optic bronchoscopy.

Studies from different lung transplant institutions have reported that the incidence of tracheal colonization by gram stain in their heart–lung or lung donors was approximately 80%.[15,29,36] Sterile bronchial secretions in donors are indeed rare. In a series of 40 heart–lung transplantations performed at Stanford between 1981 and 1986, the gram stain of the donor tracheal aspirate revealed gram-positive bacteria in 80% and gram-negative organisms in 35%. Yeast was present on staining in 25% of patients.[15] The most common organisms isolated from the tracheal aspirates were *Staphylococcus* (43%), *Candida* (23%) and *Hemophilus* (20%). Mixed aerobes and anaerobes were found in 8% of tracheal aspirates. In another study from the Washington University Group in St. Louis, 97% of bronchial washings taken from donors before retrieval grew at least one organism. The most common organisms identified were *Staphylococcus* and *Enter-*

obacter.[37] Similar organisms were isolated from the tracheobronchial tree of the recipients in 43%, and 21% of these subsequently developed invasive pulmonary infections with the same organism originally isolated from the donor.

Zenati and colleagues[38] reported that the presence of *Candida* in the donor trachea was associated with invasive candidiasis in the recipient. [38] In the same study, the only factor that was significantly associated with the onset of early infection was the presence of oral flora in the donor tracheal culture. These investigators therefore concluded that bronchoscopic lavage findings or cultures revealing oral flora are probably a marker of undetected aspiration.

Interestingly, in a small study of 9 brain-dead organ donors without clinical evidence of pulmonary infection and not on antibiotic therapy, histologic features of bronchopneumonia were seen in 7 patients (78%) on open lung biopsy specimens.[39]

Impact of an Infected Donor Lung

According to the ISHLT registry, bacterial pneumonia is one of the most common causes of early morbidity (especially in the first 2 weeks) and subsequent mortality after transplantation.[14] The overall prevalence of pneumonia occuring in the first 2 post-operative weeks in the Pittsburgh study was 33%.[29] Seventy-five percent of infections were bacterial pneumonia cases, with a mortality of 50%. According to the experience of the Toronto Group, bacterial infections were the most common cause of post-transplant pneumonia, but carried the lowest mortality compared with viral and fungal infections.[40]

Dowling and colleagues,[41] in an experimental study-using dogs, demonstrated that intravenous and aerosolized antibiotic treatment of donors with bacterial contamination prevented pneumonia in the recipients. On the basis of their study, many transplant teams now administer a broad-spectrum antibiotic treatment to the lung donor immediately prior to organ retrieval.

In clinical practice it is recommended that antibiotic coverage in transplant recipients should be initiated on the basis of gram stain results and modified on the basis of subsequent culture results obtained from donor lungs.[37]

Clinical Relevance of a Positive Gram Stain

A positive gram stain of a tracheal aspirate does not necessarily preclude lung donation. The quantity of the secretions appears to be a more important determinant of subsequent outcome. In a recent study from the University of Alabama at Birmingham, a positive donor gram stain did not predict the development of pneumonia, oxygenation or duration of mechanical ventilation after lung transplantation.[42] All recipients received standard prophylactic anti-bacterial coverage. Fourteen (16%) of 87 patients developed pneumonia in the first 30 days after transplant. Of the 43 patients with a positive donor gram stain, 5 (12%) developed pneumonia, compared with 9 of 44 (20%) with a negative donor gram stain ($p = 0.26$). The oxygenation index and the duration of mechanical ventilation did not differ between the groups.

The Toronto Lung Transplant Group was the first to mention that unilateral donor lung pathology does not preclude successful contralateral single-lung transplantation, even in the event of aspiration or purulent secretions seen bronchoscopically on the injured side.[24] Successful transplantation of single lungs, where the unused twin lung has shown signs of infection on pathologic examination, also suggests that this does not preclude use of the organ.[36]

In summary, a positive gram stain of the donor tracheal aspirate does not preclude lung donation. The amount of purulent secretions is of probable, but unproven importance.

GRAFT ISCHEMIC TIME

The upper limit of acceptable graft ischemic time is still unknown. Acceptance of graft ischemic times in excess of the 4 to 6 hours currently generally tolerated would allow for improved geographic sharing of organs and potentially improved donor lung utilization. Acceptance of longer cold ischemia times may also facilitate organ recovery from non–heart-beating donors.

Although some early reports suggested that increasing ischemic times in heart[43] and lung grafts[44] negatively impacts post-transplant mortality, other reports challenged this notion. One of the largest registry reviews by Novick and colleagues[9] of 5,052 lung transplant recipients reported an increased 1-year mortality for cold ischemic times of >6 hours when combined with older donor age (>55 years), but ischemic time alone did not increase 1-month or 1-year mortality on univariate or multivariate analysis.[9] Recent studies by Gammie et al[45] and Fiser et al[46] documented no increase in mortality for recipients with graft ischemic time >6 hours. Similarly, other studies have not shown any correlation between graft ischemic time and recipient mortality,[47-49] or between increasing ischemic time and risk

TABLE V Summary of literature for donor lung ischemic time (ischemic time >5 to 6 hours)

Reference	*n*	Design	Outcome (survival)
Snell et al (1996) (ref. 44)	63/106	Retrospective review	Reduced long term
Novick et al (1999) (ref. 9)	5,052	Retrospective review of registry data	No adverse affect except when combined with older donor age
Gammie et al (1999) (ref. 45)	60/392	Retrospective review	No adverse affect
Fiser et al (2001) (ref. 46)	15/136	Retrospective review	No adverse affect
Kshettry et al (1996) (ref. 47)	8/83	Retrospective review	No adverse affect

of acute rejection.[44,46-48] Investigators found no correlation with ischemic time and post-operative lung function (measured by days of post-operative ventilation, oxygenation or initial forced expiratory volume in 1 second [FEV_1],[45,46,50] risk of lung infection,[46] or incidence of bronchiolitis obliterans syndrome[44,46,51]). The upper limit of acceptable cold ischemia is still elusive but documentation of good post-transplant outcomes resulting from grafts with prolonged ischemia—some in excess of 6 hours and even exceeding 11 hours[45-47,52-55]—suggest that the currently observed 4- to 6-hour guideline may be too conservative using current lung preservation strategies and unnecessarily restricts the use of potentially viable organs.

In summary, the available evidence suggests few problems with grafts beyond the 6-hour ischemic time. An adverse interaction is noted with prolonged graft ischemic time and older-aged donors (Table V).

ALLOGRAFT SIZE MATCHING

Historically, size matching has been considered important in lung transplantation. In fact, several recent reports have shown that there is considerable latitude in size discrepancy between donor and recipient, but the amount of tolerable size mismatch is unknown. What are the potential complications associated with size mismatching? The use of a graft that is too small for the thoracic cavity of the recipient may result in a pleural space problem, with prolonged tube drainage and increased risk of empyema. In addition, hyperexpansion of a small graft to fill the chest cavity may reduce lung compliance and increase the work of breathing. Finally, a small graft may not provide an adequate vascular bed, with resulting pulmonary hypertension and hemodynamic compromise, particularly during exercise. These complications have been documented only in anecdotal reports,[56] however, and the fact that transplantation of single lobes is successfully performed suggests that undersizing of donor lungs does not predictably lead to major complications.

Because waiting time for patients with a small stature (e.g., patients with cystic fibrosis [CF] and female patients with emphysema) may be particularly long, it is tempting to use lungs from taller donors. However, the use of a graft that is too large for the thoracic cavity of the recipient may lead to hemodynamic compromise (thoracic tamponade) during closure of the chest at the end of the surgical procedure, and may result in atelectasis and/or distortion of airway anatomy with recurrent infection due to the impaired ability to clear secretions. In addition, recent model simulations suggest that larger transplanted lungs may perform less well than smaller ones after both single-lung transplantation (SLT) and bilateral lung transplantation (BLT), with an increased residual volume/total lung capacity (RV/TLC) ratio and a decreased vital capacity and FEV_1.[57] The frequency of these complications and the influence of factors like the degree of mismatching, presence of a pre-operative hyperinflation, and type of surgical procedure (SLT vs BLT) on their incidence is not precisely known.

Assessment of Size Matching

Various size matching criteria have been proposed, including donor and recipient chest X-ray height and width, chest (sub-mammary) perimeter, height and lung volume. Because total lung capacity, or (TLC) is a function of height, weight and gender, predicted values for the donor and recipient can be compared easily using well-established equations. Most centers now use height and/or predicted TLC as a matching criteria rather than the earlier cumbersome and unreliable methods.[58] It is important to stress that donor gender and race must be taken into account because TLC is 20% greater in males than in females and is 10% greater in white than in black patients.

Impact of Size Mismatching on Post-operative Complications and Lung Function

Studies by the Papworth Group[59,60] indicate that TLC at 1 year after heart–lung transplantation (HLT) is very close to the value predicted for the recipient, and is largely independent of the TLC predicted for the donor and of the pre-operative TLC of the recipient. In other words, post-operative TLC is more a function of the recipient predicted chest size than of donor lung size or recipient pre-operative TLC. For the 10 patients who received donor lungs that were at least 1 liter greater than their predicted TLC, the predicted donor TLC averaged 125% of the predicted recipient TLC. The corresponding figure for the 10 patients who received donor lungs that were at least 1 liter smaller than their predicted TLC was 75%. No clinical problem was reported in patients who were size mismatched to this degree. In a report on 7 patients undergoing HLT, Lloyd et al[61] described 4 patients who received lungs from donors with predicted TLCs ranging from 135% to 179% of the value predicted for the recipient. No clinical problem was noted and and again the post-operative TLC, forced vital capacity (FVC) and FEV_1 were close to those predicted for the recipient. However, 3 of the 4 patients developed an obstructive ventilatory defect 7 to 22 months after surgery, and although bronchiolitis obliterans syndrome (BOS) was the more likely reason the investigators could not exclude a role of size mismatching. They suggested that the predicted TLC for the donor should not exceed 120% of that predicted for the recipient.

Based on these data, it seems that no clinical or functional adverse effect is encountered after HLT and BLT when the donor predicted TLC is between 75% and 125% of the recipient predicted TLC. Larger organs should preferably be used for patients with pre-operative hyperinflation and smaller organs for patients with a pre-operative restrictive impairment. For recipients of SLT, no firm recommendation can be made from the available studies[62,63] however, likely for obvious technical reasons it has been suggested that "significantly larger donors" may be used in patients undergoing SLT for chronic obstructive pulmonary disease (COPD).[64]

Donor Lung Downsizing

Two groups (1 in Austria and the other in the USA)[65,66] have reported their experience with downsizing of donor lungs. In the Austrian study, which included 8 SLTs and 17 BLTs, the degree of mismatch was expressed as the ratio of donor predicted TLC/recipient pre-operative TLC; no recommendation regarding a cutoff value that would indicate the need for downsizing was given, and values for donor predicted TLC/recipient predicted TLC ratios were not provided. In case of "extreme" size discrepancy, the donor lung was split into lobes on the backtable and 1 to 2 lobes were implanted. In the presence of "moderate" discrepancies, peripheral non-anatomic resections were made in the middle lobe and lingula before reperfusing the graft. There were no post-operative complications directly attributable to the downsizing procedure.

The U.S. study reported on 11 recipients of double-lung grafts that were judged to be too large.[66] At completion of implantation, the surgeon (based on visual assessment) performed a pneumoreduction procedure to safely close the chest. The procedures included 2 right middle lobectomy procedures, 2 lingulectomy procedures, 6 combined right middle lobectomy and lingulectomy procedures and 1 right middle lobectomy combined with resection of the apices. Survival was similar in the reduced and the non-reduced group. Donor predicted TLC averaged 128% of recipient predicted TLC in the reduced group vs 108% in the non-reduced group. Interestingly, the value of 128% is very close to the value of 125% reported by Tamm et al (see earlier) in a group of 10 patients who did not undergo downsizing and yet did not develop any peri-operative complications. Otherwise stated, it is very difficult to determine whether the pneumoreduction in the study by Egan et al[66] was actually needed.

In summary, size mismatch may be important with regard to lung transplantation outcome (Table VI). The guidelines for appropriate size matching may differ for underlying disease states and for single- vs double-lung transplants. Lung reduction may be considered when utilizing grossly oversized lung donors. However, no recommendation can be made regarding the degree to which size mismatching may indicate the need for donor lung downsizing. It is likely that the need for downsizing depends on both pre-operative lung function and the difference in size between the donor lung and the recipient chest cavity (e.g., a lung from a taller donor may fit in the chest of a patient with emphysema but not in the chest of a patient with pulmonary fibrosis). The main message of these studies is that downsizing is feasible but does not significantly alter the early post-operative course nor survival.

TABLE VI Summary of literature for mismatched-sized lungs

Reference	*n*	Design	Outcome
Otulana et al (1989) (ref. 59)	20/32	Retrospective	No adverse affect (10 donors average 125% predicted recipient TLC, 10 donors 75% of recipient TLC)
Tamm et al (1994) (ref. 60)	82	Retrospective	No adverse affect (donors 75% to 125% predicted TLC of recipient)
Lloyd et al (1990) (ref. 61)	4/7	Case series	No adverse affect (donors 135% to 179% predicted of recipient TLC except obstructive defect in 3 of 4 by 7 to 22 months)

TLC, total lung capacity.

DONOR SMOKING HISTORY

Transplant Literature

There are no published studies in the field of lung transplantation that specifically address post-transplant outcomes with respect to donor smoking history. The generally accepted criterion for an ideal donor is a smoking history of ≤20 pack-years.[67] A smoking history of >20 pack-years falls into the category of a "marginal" donor. Several studies have addressed the outcome of marginal donors, but none includes sufficient numbers of >20-pack-year donors for meaningful sub-group analysis.[1,15,17-19,57,64,65] The ISHLT registry has not addressed this as a separate outcome parameter.[14] Bhorade et al.[12] from the Loyola Group assessed outcomes from the greatest number of smoking donors with 15 of 52 marginal donors having a >20-pack-year smoking history with an average of 36 pack-years overall.[2] Complications by sub-group of extended donors were detailed, but the investigators concluded that there were no clinically significant differences between sub-groups and the ideal donor group with regard to operating room (OR) complications, ICU complications, intubation time, length of hospital stay or hospital survival.

One of the major potential risks associated with the utilization of lungs from donors with a significant smoking history is the development of lung cancer in the transplanted lung. No article has provided specific commentary on this and one assumes that this was not a significant finding within the period of follow-up in these studies.

There have been no studies in the lung transplant literature reporting functionally significant emphysema, attributable to donor pathology or smoking pre-mortem, developing in transplanted lungs. Contralateral donor lung pathology has demonstrated mild-to-moderate emphysema where the twin lung has been transplanted successfully without any adverse effects attributable to initial pathology, albeit with a short period of follow-up cited.[68] Similarly, there have been few reports on lung cancer in patients who have undergone lung transplantation. The ISHLT registry does not report this as a separate entity; it is grouped under "malignancies–other."[14] The literature consists of case reports or series relating to native lung pathology with only 1 report of lung cancer attributable to donor pathology and none to donor smoking history.[69-74] There is 1 report of donor-acquired small-cell carcinoma of the lung identified as such by genetic techniques. The donor in this case had a minimal smoking history of <10 pack-years, having ceased 20 years previously.[73] A recent case series describes 2 subjects with bronchogenic carcinoma, both related to recipient factors, with 1 malignancy occurring in the native emphysematous lung in a single-lung transplant recipient, and the other attributed to an adenocarcinoma identified in the explanted lung with the underlying pathology of chronic hypersensitivity pneumonitis.[74] The largest series of bronchogenic carcinoma complicating lung transplantation described 5 carcinomas occurring in the native lung of single-lung transplant recipients and 1 in a bilateral lung recipient in whom adenocarcinoma with pleural spread was identified in the explanted lung.[75] Note that, in this last series, all recipients had a history of smoking with an average of 79 ± 39 pack-years, with 3 recipients having a >100-pack-year history. Reports of bronchogenic carcinoma in other solid organ recipients have also demonstrated a close relationship to recipient smoking history.[72] Thus, in considering the risks for developing malignancy in a donor lung with a significant smoking history, one must also weigh the pre-existing risk for the ex-smoking recipient, particularly if single-lung transplantation is to be performed (i.e., if the recipient has an extensive history of smoking, it would seem illogical to exclude a donor lung with a lesser smoking history if there had been no radiologic or

TABLE VII Summary of literature for donor smoking history

Reference	*n*	Design	Outcome (survival)
Gabbay et al (1999) (ref. 16)	5/64	Retrospective review	No adverse affect
Sundaresan et al (1995) (ref. 13)	9/44	Retrospective review	No adverse affect (sub-group not analyzed separately)
Bhorade et al (2000) (ref. 12)	15/52	Retrospective review	No adverse affect (average 36 pack-years)

No differences in short-term outcome with regard to post-operative ventilation or oxygenation, nor long-term survival to 2.5 to 3 years.

macroscopic evidence of pathology at the time of organ retrieval).

Therefore, with few data available in the lung transplant literature, a review of the literature in non-immunosuppressed subjects is warranted. The outcomes of most concern are: (1) peri-operative complications; (2) lung malignancy; and (3) long-term lung function and emphysema.

Peri-operative complications. Post-operative pulmonary complications have been described with an increased frequency in smokers, particularly with regard to thoracic procedures. However, reports suggest that smoking cessation, from as little as 10 weeks and up to 6 months prior to surgery, reduces the risk of pulmonary complications post-operatively to that of non-smokers.[76,77] This risk may be reduced after only 8 weeks of smoking cessation to 25% that of current smokers.[76] If we extrapolate this to donor lungs then we should expect minimal additional short-term complications from ex-smokers of >2 months. Active smokers undergoing cardiac and thoracic procedures have been reported to have post-operative pulmonary complication rates of 33% and 52%, respectively.[76,78] None of the articles detailed in the lung transplant literature distinguishes smoking history as "current" or "former"; however, none of the articles relating to recipients of "marginal lungs" has reported adverse short-term outcomes. Therefore, the risk of peri-operative complications in the recipient as it relates to donor smoking history is difficult to ascertain, but is unlikely to preclude the use of these lungs.

Lung malignancy. There have been several large-population studies assessing the risk of lung cancer in cigarette smokers. Most have assessed the relative risk (RR) of lung cancer in smokers as compared with non-smokers as the main outcome measure.[79-82] Three large population studies addressed the risk of lung cancer in current smokers.[80-82] Taken together, they showed an RR of 3 to 5 times that of non-smokers. One study of British doctors showed an even higher RR of 15 times that of non-smokers.[79] As expected, there was also a linear increase in lung cancer mortality based on the number of cigarettes smoked per day.[81,82] Theoretically, donor lungs of current smokers have 3 to 5 times the risk of malignancy compared with non-smokers (risk of malignancy = 0.1% per 10 cigarettes smoked per day). For those who quit smoking, the incidence of lung cancer falls according to the number of smoke-free years.[79] Importantly, the risk of lung cancer approaches that of non-smokers for those who have been abstinent for ≥20 years.[72,79,83]

COPD and lung function. The overall RR of developing COPD in susceptible individuals is dependent on the total accumulated exposure to cigarette smoke, with the highest incidence in those who began smoking before the age of 20 years.[79-82]

A linear relationship has been found between the rate of decline of FEV_1 and the number of cigarettes smoked in susceptible individuals.[84] However, several studies have shown that the accelerated rate of decline of FEV_1 associated with cigarette smoking is rapidly reversed with smoking cessation in a comparison with non-smokers.[85-87] Assuming that lung transplant recipients do not take up smoking post-transplantation, it is unlikely that the continued small decline in lung function seen in ex-smokers will become a functional problem in the lifespan of a lung transplant recipient.

In summary, the available evidence regarding the use of donor lungs with a >20-pack-year history has not reported adverse short-or long-term outcomes (Table VII).

HISTORY OF CANCER IN THE DONOR

In 1997, the Cincinnati Transplant Tumor Registry reported on 270 patients who received organs from donors with malignancies.[88] Of these patients, 107 (40%) developed tumors that were confined to the allograft or spread to distant organs. The most common donor-transmitted cancer was renal-cell carcinoma, followed by primary lung cancer, malignant melanoma, choriocarcinoma and breast cancer. Experience from the pioneering era of transplantation, when the risk of cancer transmission was not

appreciated, has appropriately led the transplant community to be circumspect and cautious regarding the use of organs from donors with active malignancies or with a remote history of cancer. Although it is obvious that this risk can never be decreased to zero at present, careful selection of donors has limited the risk of accidental cancer transmission to a small fraction of recipients.

Although the use of donors without any cancer history is preferable, some exceptions in which the risk of systemic dissemination is low or negligible have been considered acceptable. These exceptions include *low-grade skin cancer,* such as basal-cell carcinomas or many of the squamous-cell carcinomas, and *carcinoma in situ* of the uterine cervix. Primary tumors of the central nervous system (CNS) have also been considered acceptable, but several reported cases of CNS tumor transmission have recently challenged this exception.[89]

Primary CNS Tumors

Organ transplantation from donors with a primary CNS tumor is justified by the fact that these tumors extremely rarely spread outside the blood–brain barrier. However, some caution is required in considering the use of donors with primary brain tumors. First, one must be certain that it is indeed a primary brain malignancy, because in some instances autopsy examinations performed after organ harvesting have shown that the apparent brain cancer was actually a metastasis from an occult primary neoplasm. Misdiagnoses of this variety has occurred primarily with choriocarcinoma, bronchial carcinoma, renal-cell carcinoma and malignant melanoma.[88] Therefore, pre-retrieval biopsy or post-retrieval autopsy before any organ implantation is required for tissue diagnosis when a brain tumor is suspected.

Primary CNS tumors can metastasize outside the CNS in 0.5% to 2.3% of cases, and with a higher incidence in some circumstances.[90] Risk factors for CNS metastases include: (a) previous craniotomy; (b) the presence of ventricular systemic shunting; (c) high-grade tumor histology, particularly glioblastoma and medulloblastoma; (d) previous tumor radiation; and (e) a long interval between primary therapy and recurrence.[89,90] Primary malignant CNS tumors transmitted by the donor graft at the time of transplantation have been reported in 8 cases in the literature; most of these donors had undergone a previous craniotomy or radiotherapy and the tumor was a glioblastoma in 5 of 8 cases.[89] The Australia and New Zealand Transplant Registry reported no CNS tumor transmission among a total of 46 donors with CNS tumor, of which 61% were malignant and 25% had undergone a craniotomy. The United Network for Organ Sharing (UNOS) organization in the USA recorded CNS tumor as a cause of death in 188 donors from a total of 14,705 consecutive cadaveric donors, with no report of cancer transmission to date.[91,92] Hence, overall, when the histologic findings confirm a primary CNS tumor and if donors with medulloblastomas, glioblastomas, high-grade astrocytomas, or with previous invasive therapy such as craniotomy or ventricular systemic shunting are excluded, the risk of cancer transmission appears to be low, and these donors may be considered for organ donation.

Renal-Cell Carcinoma

Renal-cell carcinoma is the most common type of cancer transmitted to transplant recipients. However, the Cincinnati Transplant Tumor Registry identified a sub-group of donors presenting with a small renal-cell carcinoma, without any vascular or capsular invasion, from which the kidney could be safely transplanted after the tumor is widely excised.[93] Although data regarding outcome from organs other than kidney were not initially reported, Buell and colleagues[94] recently reported on 5 recipients of cardiothoracic organs from the same registry who received organs from donors with a renal-cell carcinoma.[94] Two tumors that presented initially with vascular invasion led to metastatic spread in the recipients, whereas 3 tumors were small and contained within the renal capsule and did not develop metastases after a follow-up of 30 to 70 months.[94]

The safety of transplanting organs from donors with small, non-invasive renal-cell carcinoma was recently questioned by Barrou and colleagues,[95] who reported cancer transmission from a small (17-mm) papillary renal carcinoma into recipients of the contralateral kidney and heart.[9] Hence, until more data are available, donors having small, non-invasive renal-cell carcinoma should not be considered for routine organ donation. However, they might be considered "marginal donors," with an acknowledged increased risk, to be used in desperate circumstances.

Donor With a Previous History of Cancer

The most difficult decision arises when the donor has a previous history of cancer treatment. Although it is clear that donors with active malignancies, other than the few exceptions just cited, are considered unacceptable for organ donation, the risk of cancer

TABLE VIII Summary of literature for donors with a history of malignancy

Acceptable:
- Low-grade skin cancer (basal cell and squamous cell)
- Carcinoma in situ of organs such as the uterine cervix
- Primary tumors of central nervous system
  - If there are risk factors for metastases consider organs as marginal, including:
    - High-grade histology
    - Glioblastoma and medulloblastoma
    - Previous craniotomy
    - Ventricular shunts
    - Tumor radiation
    - If there is recurrent disease in the brain, or a long interval from primary therapy

Not acceptable (consider as marginal if previous treatment with presumed cure)
- Renal cell cancer
- Lung cancer
- Melanoma
- Choriocarcinoma
- Breast cancer
- Colon cancer

transmission from donors with a past history of malignancy remains unknown. The only data available were derived from the UNOS Transplant Tumor Registry, which reported on 257 donors with a past history of malignancy, and no observed tumor transmission among a total of 650 recipients.[92] Unfortunately, the initial staging of the tumor was not known and histology was reported in only 88 of those donors. In addition, 85% of the donors had a history of cancer from the skin, brain or genitourinary tract, which present a low risk of cancer transmission. Cancer transmission from a breast and a colon cancer after an 8- and a 5-year apparent cancer-free interval, respectively, has been reported, demonstrating the potential risk of transmission even after a prolonged period of remission.[96] Currently, considering the data available, all donors with a past history of cancer other than skin and brain tumors should be considered at increased risk, and the decision as whether or not to use the organs should be made on an individual basis.

In summary, the potential risk of cancer transmission from recipient to donor is largely based on histology, stage of tumor and length of cancer-free survival (Table VIII).

ABO INCOMPATIBILITY

Background

ABO incompatibility between donor and recipient has always been considered an absolute contraindication to solid organ transplantation, but not to grafting of tissues such as skin and cornea.[97] Patients transplanted with organs from ABO-incompatible donors will likely develop hyperacute rejection. The immediate immune reaction between circulating recipient-derived antibodies and antigen-presenting cells in the donor organ will trigger an acute inflammatory reaction that leads to widespread thrombotic vascular occlusion of the graft. Sensitized ABO-identical recipients may also experience hyperacute rejection, and therefore a prospective lymphocytotoxic crossmatch is advisable in potential transplant recipients with known HLA antibodies.[98]

ABO-Compatible Donors

Lung transplantation, unlike other solid-organ transplants, involves transplantation of a large amount of lymphoid tissue. Hence, there is potential for graft-versus-host reaction if there is an antigen mismatch between donor and recipient.

Therefore, in lung transplantation ABO-identical organs are generally preferred, but occasionally the use of an ABO-compatible, but non-identical donor is clinically warranted. In these recipients, hemolysis by donor-derived red blood cell antibodies may occur and become a serious problem.[99-103] A post-transplantation policy of using donor ABO group red blood cells in these ABO-compatible lung recipients may prevent this problem.[100]

In one study from the Cleveland group, outcome after lung transplantation was compared between ABO-identical and ABO-compatible lung transplant recipients.[104] No difference in reperfusion injury, ICU and hospital stay, incidence of acute and chronic rejection as well as survival at 1 year could be demonstrated between groups. The investigators

therefore concluded that identical blood group may not be necessary for lung transplantation, thus removing one of the constraints for matching donors to recipients. This policy may have an impact in the process of lung transplant allocation.

In an ISHLT registry analysis by Novick and colleagues,[105] looking at the outcome of 139 pulmonary retransplants, an identical ABO match was one of the factors associated with a small, but statistically significant survival advantage by univariate analysis.

Rhesus Mismatch

The same problem of severe hemolysis may occur in Rhesus (Rh)-positive lung transplant recipients who received an organ from a previously isoimmunized Rh-negative donor presenting anti–D antibodies.[2]

In summary, the available evidence does not suggest any significant disadvantages in using ABO-compatible rather than non-identical lung donors.

THE ASTHMATIC DONOR

There is a paucity of information on the use of lung allografts harvested from donors with a history of asthma. The English-language medical literature includes only 2 articles describing a total of 3 recipients of lungs from asthmatic donors. The available information is summarized in what follows.

Ghosh and colleagues[106] reported the development of acute airway obstruction in a patient who received a heart–lung bloc from a 15-year-old asthmatic boy. Ostensibly the donor was mildly asthmatic and required only occasional treatment with an inhaled β-agonist. During the period of mechanical ventilation prior to harvest of the organs, there had been no requirement for bronchodilator therapy and peak airway pressures did not exceed 20 cm H_2O. Although the explanted lungs were observed to not fully deflate, implantation was successfully carried out. The initial attempt to ventilate the lungs after reperfusion resulted in minimal inflation despite peak airway pressures in excess of 50 cm H_2O. The recipient received intravenous isoproterenol, salmeterol and methylprednisolone. Bronchoscopy was performed, revealing constricted airways diffusely filled with mucus plugs. After therapeutic lavage, ventilation was successfully reinitiated with full inflation/deflation and acceptable peak airway pressures. The investigators attributed the episode to a combination of bronchospasm and mucus plug formation, seemingly resulting from the asthmatic predisposition of the transplanted lungs.

Corris and Dark[107] described 2 non-asthmatic recipients who received heart–lung blocs from asthmatic donors. Available history on the donors suggested that they had mild asthma, managed in 1 case with β-agonists alone and in the other with β-agonists and inhaled steroids. Both recipients of the asthmatic lungs demonstrated exaggerated diurnal variation in peak expiratory flows (in excess of 30%), with early morning "dipping." In both cases, onset of this phenomenon was within 1 week of transplantation. Transbronchial lung biopsies revealed mild eosinophilic infiltrates in the airways, but no evidence of acute rejection or bronchiolitis obliterans. Both patients demonstrated a favorable response to inhaled β-agonists and inhaled steroids. One patient subsequently demonstrated histologic evidence of bronchiolitis obliterans at 8 months post-transplantation.

Although Corris and Dark concluded that the asthmatic profile of the recipients reflected persistence of asthma conveyed by the donor lungs, this interpretation is confounded by the observation of non-specific bronchial reactivity in the general lung transplant population. Morrison et al[108] and Higgenbottam[109] pointed out that increased diurnal variation of FEV_1 was observed after heart–lung transplantation involving non-asthmatic donors, although this was in the context of acute rejection.[108, 109] More recently, Stanbrook and Kesten demonstrated positive methacholine challenge testing in 30% of lung transplant recipients at 3 months after surgery.[110]

Asthmatic donors were used on 2 occasions at the University of Pennsylvania.[111] In 1 case, a recipient of a single lung from an asthmatic donor developed acute bronchospasm intraoperatively upon commencement of ventilation of the freshly implanted allograft. In the other case, a marginal donor was chosen with a lifelong history of asthma and remote history of intubation who more recently was reported to have only mild symptoms, which were controlled with inhaled bronchodilators and inhaled steroids. Two patients with underlying severe chronic obstructive lung disease, who were deemed unlikely to tolerate a wait for another more suitable donor, each received a single lung from this donor. Although the early post-operative period was uneventful, both recipients demonstrated persistent severe airflow obstruction on spirometry obtained at 3 months post-transplantation, with an FEV_1 of 22% and 33% of predicted, respectively. No alternative cause for the severe airflow obstruction was identified. Neither patient improved significantly with institution of high-dose inhaled corticosteroids and β-agonists or with courses of high-dose systemic

steroids. These investigators concluded that the donor probably had fixed airways remodeling from long-standing asthma, although there is no histologic support for this conclusion at present.

In summary, based on anecdotal reports, the use of allografts from asthmatic lung donors may be associated with poorer short- and long-term functional outcomes.

LENGTH OF MECHANICAL VENTILATION

Prolonged endotracheal intubation and mechanical ventilation of the donor may affect acceptability by increasing the risk of ventilator-associated pneumonia and ventilator-induced lung injury. Data related to the impact of these factors in lung transplantation are scant. Greater than 2 days of mechanical ventilation is an independent risk factor for ventilator-associated pneumonia (VAP) and the crude rate of VAP has been estimated as 1% to 3% per day of intubation and mechanical ventilation.[112] Longer donor mechanical ventilation does not directly equate with poor post-transplant graft function, however, and when considered alone should not preclude donation. Donors intubated for >5 days with good oxygenation, clear chest radiograph, unremarkable sputum gram stain and bronchoscopic exam may in fact be more acceptable for lung transplantation than donors intubated only briefly after traumatic brain death because sequelae of complications such as aspiration, and pneumonia may be more difficult to detect within the first 24 to 48 hours. Ciulli et al[115] reported that the utilization of donors as long as 15 days after initial intubation was not associated with an increase in recipient infection with donor identified organisms, again indicating that donors should not be excluded based solely on length of mechanical ventilation.

In summary, the evidence does not suggest length of donor mechanical ventilation is important in lung transplantation outcomes.

CAUSE OF DONOR DEATH

Although it has been speculated that the cause of donor death may influence the long-term outcome of the transplant, there has been only one retrospective study revealing a higher incidence of both acute and chronic rejection from traumatic brain-death donors as compared with recipients of causes other than brain death.[114] Brain injury may lead to up-regulation of proinflammatory cytokines, potentially affecting the donor lung and having an influence on the amount of ischemia–reperfusion injury. The cause of death of potential lung donors may impact their acceptability, particularly in cases of trauma where the lungs may have been damaged with contusions, parenchymal lacerations, bronchial fracture, hemorrhage, pulmonary edema or thromboemboli. Indeed, data from the U.S. Scientific Registry of Transplant Recipients recorded head trauma as the most common cause of death.[115] Regardless of the cause of donor death, resuscitation efforts may also cause damage to donor lungs. Cardiopulmonary resuscitation (CPR) or chest tube insertion may cause mechanical parenchymal damage. Large quantities of intravascular volume replacement with blood products or crystalloids may lead to pulmonary edema, leaving the lungs unsuitable for transplantation. However, there are few data published to support these concerns and, in the absence of overt evidence of dysfunction, organs are generally recovered from these donors.

In summary, cause of donor death may relate to long-term outcomes from lung transplantation, but further studies are warranted to better define this relationship.

GENDER

Background

There is no particular gender matching in lung transplantation and the effects of gender on donor and recipients are largely unknown. However, due to lung-size considerations, large male recipients more often receive lungs from a male than a female donor. Smaller recipients are more often females and more often receive smaller female lungs. Victims of fatal traumatic head injuries are more often males, and most of these donor lungs are given to male recipients.[116] In this way, gender may indirectly affect outcome in that the issues related to mode of brain death, discussed earlier, may play a disproportionate role in males.

There may also be a direct effect of gender. It is well known that gender-associated hormones can modulate immune responses and, consequently, influence outcome; this is believed to be the case in infectious and autoimmune diseases. In general, estrogen suppresses T-cell–dependent immune functions and enhances B-cell function and antibody production. The glucocorticoid response to stress is inhibited by androgens, but enhanced by estrogens.[117] In contrast, the glucocorticoid sensitivity of target tissues was found to increase 1 hour after stress in men, but decrease markedly in women.[118]

Interleukin-2 (IL-2) plays an important role in adaptive immune responses, particularly in acute rejection. Estrogen suppresses IL-2 production at

the transcriptional level by decreasing the important IL-2 promoter transcription factors NF-κB and AP-1.[119] In addition, 17β-estradiol inhibits IL-2 receptor expression in activated T cells.

Clinical Studies

In the latest data set of the ISHLT registry,[14] a risk factor analysis for bronchiolitis obliterans within 3 years after lung transplantation was performed. Female donor status was associated with decreased bronchiolitis obliterans, with an odds ratio of 0.79 ($p = 0.01$). In contrast, in a multivariate analysis investigating the predictors of successful organ donation, female gender was not an independent predictor.[120]

In summary, gender does not have an obvious impact on long-term outcomes of lung transplantation.

Conclusion

Generally accepted lung criteria can now be considered based on broad clinical impressions rather than solid medical evidence. The ultimate judgment as to whether a donor lung is used for transplantation is made on the basis of donor and recipient factors in each individual case. With the evolution of clinical lung transplantation over the past 20 years, experience has demonstrated that many more organs can be utilized for transplantation than would be the case if the original criteria for lung donation were strictly adhered to. There is a clear need for extension of the traditional donor criteria to help ease the profound shortage of donor lungs. However, follow-up studies are necessary to validate the safety and efficacy of broader acceptability criteria. If we can increase the utilization of currently available potential lung donors, this will have a significant impact on the imbalance between transplants performed and rate of deaths while on the waiting list.

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