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Review

Lung Donor Selection and Management: An Updated Review

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Abstract

The shortage of donor lungs for transplantation is a major challenge, resulting in longer waitlist times for patients with a higher risk of waitlist mortality. It is crucial to continue promoting awareness about organ donation through legislation, public campaigns, and health care provider education. Only a small number of cadaveric donors meet the ideal criteria for lung donation, leaving many lungs unused. Donor lung utilization can be improved by carefully considering the extended-criteria donors, actively participating in donor management, and by utilizing the modalities to assess and manage the marginal lungs after retrieval from the donor. The purpose of this article is to provide an up-to-date review of donor selection, assessment of donor lungs, and donor lung management to enhance organ recovery rates for lung transplantation.

Keywords
Lung transplantation; brain dead donor; donor selection; donor management

1. Introduction

Lung transplantation (LTx) is a lifesaving treatment option for patients with end-stage lung disease, for whom all other medical treatment options have been exhausted. The increasing number of patients with end-stage lung disease and the growing number of lung transplantation surgeries necessitate the need to expand the donor pool. Since the very first lung transplant in 1963, there have been several advances in the field of lung transplantation, including surgical techniques, immunosuppression, post-transplant management, and diagnostic testing, all of which played a vital role in improving short- and long-term outcomes. One of the challenges that we continue to face is the donor lung shortage, which results in longer waiting times and higher waitlist mortality [1, 2].

2. Donor Assessment and Selection

The standard criteria for ideal donor lungs is (1) age <55 years (2) ABO compatibility (3) a clear chest radiograph (4) partial pressure of oxygen >300 mm Hg on a fraction of inspired oxygen of 1.0 and a positive end-expiratory pressure of 5 cm H_2O (5) a cigarette smoking history of ≤20 pack-years (6) the absence of chest trauma (7) no evidence of aspiration or sepsis (8) no prior cardiopulmonary surgery (9) a sputum gram stain negative for organisms and (10) the absence of purulent secretions on bronchoscopy. However, only 15-20% of lung donors are standard or ideal donors. Hence, extended criteria lung donors including age 55 years and above, PaO_2 <300 mmHg at 1.0 FiO_2 and PEEP 5, cigarette smoking history of >20 pack years, inhalation drug abuse, and the presence of infiltration on chest X-ray or purulent secretions at bronchoscopy are being increasingly utilized. We also utilize donors with prior cardiothoracic procedures. The short-term and long-term survival are comparable with and without a prior cardiothoracic procedure [3].

Proper donor selection and management is imperative to mitigate the risks of early post-transplant complications, primary graft dysfunction (PGD) and thereby rejection rates. PGD, as a consequence of ischemia-reperfusion injury, is responsible for nearly one-third of early deaths within the first 30 days post LTx [3, 4]. It is commonest reason for prolonged need for mechanical ventilation, longer ICU stay and potential cause for baseline lung allograft dysfunction. Multiple factors including donor's smoking history, clinical course at the time of organ allocation, mode of lung preservation, as well presence of pulmonary hypertension (PH) in the recipient are implicated in the development of PGD. Minimizing the risk of PGD through proper donor selection and appropriate donor management is crucial for successful lung transplantation outcomes.

2.1 Donor Age

The standard criteria consider the age of 55 or less as the ideal donor age for lung transplantation. Per the extended criteria, donors up to the age of 65 years can be considered, and the retrospective studies have shown comparable outcomes in terms of both survival and freedom

from chronic lung allograft dysfunction [5, 6]. Utilization of lungs from donors greater than 70 years of age have shown encouraging results. A single-center study showed similar 1-year survival while larger studies showed increased mortality [5-7]. Lung transplant recipients with cystic fibrosis were noted to have inferior survival and a longer ICU length of stay when receiving organs from donors 55 years or older. The interplay of donor age and recipient age was assessed by Chaney et al, who showed that donors older than 50 years have increased the risk of death for recipients younger than 60 years compared to recipients older than 60 years [5, 8]. In a study of 647 bilateral lung transplants, 69 patients received lungs from donors aged 70 or older (mean age: 74 years; range: 70-84 years) compared to a matched younger group with a mean age of 49 years (range: 12-69 years). No significant differences were found in the duration of ventilatory support, ICU, or hospital length of stay. PGD-3 occurred in 26% of the older group and 29% of the younger group ($p = 0.85$). Re-intervention rates were comparable (29% vs. 16%; $p = 0.10$). Bronchial anastomotic complications showed no difference ($p = 1.00$). Five-year patient survival rates were 73.6% for older donors and 73.1% for younger donors ($p = 0.72$), while CLAD-free survival rates at five years were 51.5% for older donors and 59.2% for younger donors ($p = 0.41$), without significant differences [9].

2.2 Donor Gender

There is a considerable lack of clarity concerning gender selection for lung donors. While some studies have shown increased survival and decreased bronchiolitis obliterans in opposite-gender transplants, i.e., male (M) to female (F) or F to M, the ISHLT registry review from 1995–2002 showed increased mortality in F to M transplants. F-to-F transplants have also been shown to improve both short- and long-term survival [6, 7].

2.3 Donor Race

A retrospective study of lung transplants from 1997 to 2007 with donors and recipients who were matched by race revealed a decrease in risk-adjusted mortality of 3.3% at 5 years and a 12% mortality in those recipients who were suffering from idiopathic pulmonary fibrosis (IPF), cystic fibrosis (CF), or a single lung transplant [8]. Matching recipients and donors by race conferred no change in one-year rejection rates. Lungs from donors of African American origin imparted an increased risk of death to the recipient irrespective of recipient variables; however, the recipient race was not found to have an association with variability in survival [10].

2.4 Smoking History

Using lungs from donors with a smoking history raises the concerns for potential obstructive pulmonary disease and the risk of transplanting undiscovered cancer or metastases or the risk of developing a malignancy in the future [11, 12]. To minimize these risks, in depth chest imaging (chest X-rays and CT scans when available) and bronchoscopy examination of the lung during the donor assessment and if needed, biopsy of any suspicious areas must be performed at the time of organ retrieval [12]. It has been shown that the donor's smoking history affects early outcomes, but not necessarily the late outcomes after transplantation [13]. There is currently no information on the safe amount of cigarette smoke exposure for a donor before their lungs are considered unsuitable for transplant, acknowledging that overall outcomes are dependent on the amount of

the cigarette smoke exposure. Despite these uncertainties, a history of smoking should not automatically exclude a donor's lungs from being used for transplantation. Apical blebs that are often seen with a history of smoking cigarettes or marijuana, can typically be resected during the transplant procedure [14]. On availability of donors with a smoking history of more than 20 pack year, a careful assessment of the lung parenchyma on CT to assess for any emphysematous changes or suspicious lesions and an assessment of the respiratory mechanics on the ventilator might guide us better in making the decision to accept or not.

2.5 Oxygenation

Measurement of PaO_2 on 100% FiO_2 and positive end-expiratory pressure (PEEP) of 5 is one of the quality–assessment measures that has been traditionally being used to predict the allograft function post-transplant. A cutoff greater than 300 meets the standard donor criteria. However, a UNOS database study by Zafar and colleagues showed that donor PaO_2 did not affect the graft survival, irrespective of laterality of the transplant [5, 8]. Whitford et al in their study, did not notice any differences in the time to extubation, incidence and severity of PGD, graft function and 1-year survival, between the recipients who received lungs with PF ratio <300, compared to recipients who received lungs with a PF ratio >300. Atelectasis in donors with high BMI contributes to a lower PF ratio, and such lungs can be utilized for transplantation via either intraoperative lung recruitment using positive end-respiratory pressure of 25 to 30 cm H_2O for 30 seconds or ex vivo lung perfusion.

2.6 Size

In the process of donor assessment and selection, size matching is crucial. Although several size-matching criteria have been put forth, predicted total lung capacity (pTLC), which is determined by sex and height, is the most popular one [15, 16]. Even though actual total lung capacity (TLC) measurements assessed by plethysmography provide correct approximations of lung volume, this testing is not feasible for organ donors. [17]. As an objective measure, an alternative proposal suggests determining an individual's predicted Total Lung Capacity (pTLC) by considering age, height, and gender as determining factors. [17-19]. Donor’s pTLC can be calculated. For males: pTLC = 7.99 × height (m) - 7.08. For females: pTLC = 6.60 × height (m) - 5.79. Recipient's lung disease, actual total lung capacity (aTLC) and pTLC should be compared with the donor’s pTLC. A donor pTLC between 75% and 125% of the recipient pTLC does not cause any adverse clinical or functional effects and, therefore, is considered acceptable for safe use [20]. This wide range of acceptable lung sizes implies that the chest wall can adapt to the newly implanted lungs [21]. However, it is important to acknowledge that pTLC ignores the crucial elements such as weight, race, and the underlying cause of the recipient's lung disease that determine the chest cavity size. Effective and ideal size matching in transplantation entails considering anatomical factors when comparing the volume of the donor lungs with the recipient's thoracic cavity's available space. Therefore, a more precise technique such as 3D CT volumetry can guide the clinicians better in predicting and matching the size of donor and recipient lungs. By identifying lung tissue and nearby chest wall voxels, computed tomography (CT) volumetry measures lung volume and provides a more accurate representation of actual lung size for determining the suitability of donors [22]. Computed tomography (CT)-acquired lung volumes may be successfully employed for size matching in lung transplantation by utilizing cutting-edge segmentation algorithms. Compared to existing

approaches that only include variables like gender and height, this technique shows promise in terms of better outcome prediction [23]. In a single-center study by described by Shepherd et al [24], a pre-operative CT volumetry facilitated the confident acceptance of donor lungs that were initially predicted to be oversized based on other clinical measures. Similarly, promising results were reported with the use of 3D volumetry in a study by Fujimoto et al [25] wherein measurement of recipient chest volume by 3D-CT volumetry helped surgeons downsize lung grafts and accurately calculate the appropriate volume of reduction prior to transplantation.

Pediatric patients with unusually small chests may be candidates for lobar or split-lung transplantation or peripheral non-anatomical wedge resections of the donor lungs [26, 27]. If the donor lungs are significantly larger than the recipient's lungs, lung reduction can also be performed using commercially available staplers before closing the chest. The post-transplant outcomes of such cases remain the same despite these additional procedures [28].

2.7 Active Infection

Donor's airway samples often have positive sputum gram stain and cultures. Timely identification of the organism, obtaining the organism susceptibilities and the appropriate antimicrobial therapy will help manage the donor effectively especially in those donors with evidence of infiltrates or consolidation on the imaging. However, it has been shown that post-transplant pneumonia, oxygenation, or the duration of mechanical ventilation are not predicted by a positive donor gram stain [29-31]. According to a study by Ruiz et al, 52% of lung donors had active infections, and 8.1% of those cases resulted in transmission to the recipient despite the use of the recommended antibiotic prophylaxis [32]. Lower airway colonization may be a sign of an elevated risk for postoperative graft infection and dysfunction, according to Newcastle group research that found poor early graft performance and reduced survival in patients with positive donor bronchoalveolar lavage (BAL) cultures [33]. Frequent airway sampling and targeted antimicrobial therapy against the detected organisms are necessary for optimal transplant outcomes.

2.8 Donor Malignancy

Transmission of cancer from donor though rare can have serious consequences. Clinical evaluation, high-quality imaging and when feasible autopsy of donor in after organ donation depending cause of death are crucial [34]. In donors with a history of malignancy, it is vital to obtain the complete history of the malignancy including the type, staging, year diagnosed, treatments received, history of recurrence, as such history will help the clinicians to predict the risk of transmission to the recipients.

The use of immunosuppression accelerates tumor dissemination and treatment of malignancies post-transplant can be challenging with devastating and fatal consequences. Except in rare circumstances where the risk of tumor transmission is deemed to be extremely low (basal cell skin cancers, some squamous cell cancers, in situ cervix carcinomas, certain primary central nervous system tumors, excluding medulloblastoma, glioblastoma, and high-grade astrocytoma), the use of a donor with an active malignancy is not recommended [35].

3. Donation After Circulatory Death (DCD)

The use of DCD donor lungs significantly enhances the transplant activity for many lung transplant programs across the world, reducing waitlist mortality and waiting list duration. Some facilities report a sizable percentage of patients receiving DCD donor lungs (Australia: 28%; Netherlands: 40%; London: 25%; Canada: 32%) [36-38]. It is essential to remember that DCD and DBD lung donors differ in several biological, legal, and procedural ways. The Maastricht classification was created to account for these variations since circulatory death can occur in a variety of situations and that can affect how severe the ischemia injury is to the donor lungs. In nations where medically assisted circulatory death is permitted, like Belgium and the Netherlands, a change has been suggested that would permit euthanasia under Category V [39, 40]. It's critical to understand the difference between managed and uncontrolled DCD since the latter situation raises the risk of lung damage. In controlled DCD, cardiac and ventilatory support are intentionally removed in a controlled setting. The outcomes of lung transplantation utilizing DCD donors are equivalent to those obtained with DBD donors [41, 42].

4. Donor Risk Criteria

Per CDC analysis, there was more than two-fold risk in the increased risk donors of 9.3% to 26.2% from 2010 to 2017 [43].

To increase the organ utilization rate while ensuring the transplant recipient safety and outcomes, it is crucial to assess the donor for any risk factors that can result in transmission of infections such as HIV, HBV and HCV. OPTN in collaboration with PHS defines the donors with risk criteria and has policies in place to screen the donors and the recipients if they receive an organ from such donors. It is highly important for the transplant centers to have protocols and pathways in place if a recipient acquires donor derived infection. Per PHS 2020 updated guidelines, it is recommended not to use the term “increased risk donor” rather to refer to “risk criteria” present or not.

All potential organ donors are tested for HIV, HBV, HCV. NAT and serological tests are performed in every donor irrespective of the risk criteria.

Following criteria, if present within the 3 months of organ procurement, would categorize the donor with risk criteria.

i. Sex with a person known or suspected to have HIV, HBV, or HCV infection.
ii. Man who has had sex with another man
iii. Sex in exchange for money or drugs
iv. Sex with a person who had sex in exchange for money or drugs.
v. Drug injection for nonmedical reasons
vi. Sex with a person who injected drugs for nonmedical reasons.
vii. Incarceration (confinement in jail, prison, or juvenile correction facility) for ≥72 consecutive hours
viii. Unknown medical or social history
ix. Child born to a mother with HIV, HBV, or HCV infection.
x. Child breastfed by a mother with HIV infection.

Per CDC study, the risk for undetected infection in donors with risk criteria present, when screened by NAT 30 days after the most recent risk behavior was less than 1 per million for HIV, HCV and HBV infection [44].

5. Hepatitis B Donors

Utilizing hepatitis B core antibody positive (HBcAb+) donors is one strategy to increase available organs [45]. The use of HBcAb+ donors and recipients with hepatitis B vaccination seems to be safe with comparable outcomes. Very few studies have reported use of HBsAg positive donors for lung transplantation. However, one study by Belga et al, noted that the use of HBsAg-positive donors must be considered in urgent thoracic transplantation; good short-term outcomes with combination of antiviral therapy and HBIG have been attained. Emphasis should be laid on the strategies for monitoring of these recipients as well as the duration of antiviral prophylaxis required. [46].

6. Hepatitis C Donors

Historically, hepatitis C virus (HCV) infection was considered a contraindication to organ donation due to an approximately 100% transmission. In the current opioid crisis, the availability of second generation direct-acting antiviral (DAA) medications made it possible to utilize Hep C donor organs. Cypel and colleagues compared the outcomes in recipients of lungs from 22 donors who were HCV NAT Positive (HCV+) with outcomes of recipients of lungs from 187 HCV NAT negative (HCV-) donors. All the lungs from HCV+ donors were placed on EVLP (ex vivo lung perfusion) prior to transplant. Almost all recipients (90%) of lungs from HCV+ donors developed HCV viremia within one week of transplantation, and these patients then underwent 12-week treatment with DAAs. Two patients had a relapse of HCV viremia and required further treatment to eventually achieve a sustained virologic response. 6-month survival (95%) of the recipients from HCV + donors was similar to the survival of recipients of lungs from HCV- donors (94%). Waitlist time was significantly shorter for the recipients of lungs from an HCV+ donor. Other variables, including primary graft dysfunction, length of hospital stay, intensive care unit stay, and incidence of acute rejection, were also not significantly affected using an HCV+ donor and DAA therapy post-transplant [45].

Similarly, a UNOS database study comparing outcomes of lung transplants in 189 patients who received lungs from HCV+ donors with 9511 recipients who underwent lung transplant using lungs from an NAT-negative donor found no differences in survival up to one-year post-transplant or in any of the other outcome indicators evaluated, which included graft failure, airway dehiscence, acute rejection, or reintubation [47]. Recently, it has been shown to have physical viral clearance in combination with germicidal light-based therapies using normothermic ex-vivo Lung Perfusion (EVLP).

7. COVID-positive Donors

Around 177 million COVID-19 instances have been reported globally, many of whom could potentially be organ donors. In parallel, the demand for donor lungs has risen because of broadening indications including COVID 19 related end stage lung disease. Considering that COVID-19 most frequently affects the respiratory system, it is necessary to establish rigorous donor

assessment standards and demonstrate the safety and utilization of lung donation after COVID-19 infection. The collection site of the samples also has an impact on the Ct values and load of SARS-CoV-2 detection [48, 49]. The most precise and detailed swab location for COVID-19 diagnosis was the nasopharynx, followed by the throat [50]. In comparison to throat specimens, higher virus loads were seen in nasal samples [51]. Sputum and BAL samples have demonstrated better sensitivity in contrast to upper respiratory samples, which is likely because they contain large virus loads [52].

Utilization of RT-PCR Ct values in conjunction with the donor history and chest imaging can guide the clinicians to assess the suitability of the organs for transplantation and to predict the possible transmissibility of COVID 19 infection from donor to recipient. Hwang and his group studied the outcomes of utilizing the lungs from asymptomatic incidental COVID 19 positive donors. Donors with positive NP RT-PCR and Ct value of less than 35 were declined for lungs. Donors with positive NP RT-PCR and Ct value greater than 35 were further tested for lower respiratory tract RT- PCR and those with positive LRT RT-PCR were declined for lung transplantation. There were 8 NP RT-PCR COVID positive donors with Ct less than 35, from whom lungs were utilized for transplantation. There was no documented transmission of COVID-19 from donors to recipients. 30- and 90-days survival was 100% [53].

Following are the ISHLT COVID-19 Task Force consensus recommendations for the deceased donor

i. pre-transplant COVID-19 symptom assessment is recommended. Donor e with an active clinical syndrome compatible with COVID-19, regardless of known exposure within the past 10 days and negative PCR test results, should be avoided.
ii. testing for SARS-CoV-2 RNA by nasopharyngeal/oropharyngeal swab, sputum/tracheal aspirate, bronchial wash, or bronchoalveolar lavage (BAL) less than 72 hours before organ donation is recommended.
iii. a deep respiratory specimen (bronchial wash, BAL, mini-BAL, or tracheal aspirate) for SARS-CoV-2 RNA for all lung donors is strongly recommended.
iv. thoracic CT scan should be considered for donor assessment and possible risk of COVID-19 in donors.
v. Antigen test is not acceptable for donor evaluation.
vi. COVID-19 vaccination status of the donor does not alter these recommendations.
vii. For a donor with Exposure to confirmed or suspected case of COVID19 within past 10 days, organ may be considered for transplant if donor has been asymptomatic and is more than 7 days following exposure and gas at least one negative SARS-CoV-2 PCR test has been performed on a lower respiratory sample within 24 hours of transplant and has CT chest has been performed and has shown no evidence of pulmonary infection and for a potential recipient candidate has a high risk of death without organ transplantation.
viii. For Donor with prior confirmed COVID-19 may be considered for transplant if there is clinical resolution of symptoms due to COVID-19 and is >21 days from the onset of symptoms in an immunocompetent donor without significant pulmonary disease due to COVID-19 (for e.g., required intubation) and at least one negative RT-PCR and CT chest negative for evidence of pulmonary infection/chronic lung injury. A lower respiratory sample for SARS-CoV-2 is strongly recommended for all lung donors [54].

8. Donor Management

Less than 13% of all brain-dead donors are utilized to harvest and transplant lungs [55]. Judicious assessment and management of donor lungs is of utmost importance to increase their utilization rate. An attempt to allocate multiple organs from a donor can result in certain antagonistic management strategies to maintain organ perfusion and to prevent organ injury.

For example, a restrictive fluid balance is associated with higher rates of lung procurement, whereas aggressive volume repletion facilitates the maintenance of kidney function. Utilization of high PEEP (>10 cm H_2O) or alveolar recruitment maneuvers with PEEP over 16-20 cm H_2O may prevent volutrauma and atelectrauma but might negatively affect the donor's hemodynamic status. An intensive lung donor treatment protocol is based on multiple synergistic parameters, such as protective ventilation, recruitment maneuvers, utilization of high PEEP, fluid restriction (including the use of diuretics) with reduced target extravascular lung water (EVLW) values, the use of invasive cardiac output measurement to guide fluid and catecholamine administration, and, finally, the use of steroids after brain death diagnosis. This protocol has been validated in a multicenter study, and applied in all types of centers, both with and without lung transplant programs (LTPs). Lung donors, lung grafts retrieved, and the number of lung recipients transplanted were more than doubled with this protocol [55-60].

The goals of management of donors include optimizing cardiac filling pressures, maintaining adequate arterial pressure for donor organ perfusion, ensuring a patent airway, ensuring lung protective ventilation strategies, and maintaining metabolic homeostasis [61-63].

8.1 Monitoring

Arterial and central venous lines aid in the monitoring of the donor's hemodynamic condition. A pulmonary artery (PA) catheter is also preferred in donors with low mean arterial pressure (MAP less than 60 mm Hg) but appropriate central venous pressure (CVP) (CVP of 6-10 mm Hg) [63, 64]. Arterial blood gases, chest radiographs, computed tomography scan of the thorax, end-tidal carbon dioxide monitoring and bronchoscopies should be performed at regular intervals. Lung compliance should be monitored on a regular basis as any decline in compliance in conjunction with any of the abnormal testing can guide the clinicians in assessing the lung pathology, if any.

8.2 Ventilatory and Airway Management

Protective lung ventilation by limiting the tidal volumes of 6-8 ml per kg IBW, lowering the driving pressures, utilizing the appropriate PEEP (8-10 cms H_2O) and avoiding higher peak airway pressures of >35 mm Hg, is preferred to prevent barotrauma or volutrauma. Regular endotracheal suctioning and gentle recruitment maneuvers are often considered. Arterial blood gases should be obtained regularly to monitor for hypoxemia and or acidosis and if present, should be addressed and corrected promptly. Also, it is preferred to limit the PO_2 to less than 500 millimeters of mercury to limit the subsequent bronchiolitis obliterans in lung transplant recipients. Endotracheal tube cuff needs to be appropriately inflated, adequate to prevent any aspiration. Bronchoscopy needs to be performed to examine the airways for any lesions or inflammation trauma of for any mucopurulence, and to assess for any aspiration and to obtain airway (bronchial washing or Broncho alveolar lavage) samples to assess for infection.

It is not unusual to encounter atelectasis, secretions, infection, and inflammation in the donor lungs which along with the gravitational forces, increase the risk for ventilation perfusion mismatch that can result in hypoxemia. Avoidance of hypervolemia, use of appropriate antimicrobial therapy, use of diuretics and utilization of recruitment maneuvers play a vital role in mitigating hypoxemia. Prone positioning, airway clearance, judicious fluid management and recruitment maneuvers have been shown to improve lung compliance [65].

Assessment of lung compliance at bedside prior to the organ retrieval or before the chest is open has its own set of advantages and disadvantages. It cannot be relied on as a sole marker to assess the quality of lungs as it can be affected by extrapulmonary factors such as pleural effusion, chest wall, endotracheal tube size, airway obstruction or mucus plugging. When trended and used in conjunction with arterial blood gas, CT Chest and bronchoscopy findings it can guide the clinicians in assessing the quality of the donor lungs.

Deflation test is a routinely performed intraoperative maneuver during lung procurement, to assess compliance. Benazzo and colleagues assessed the lung compliance at the time of flung retrieval in the operating room and noted that dynamic compliance (Cdyn) (PIP - positive end-expiratory pressure/tidal volume) is a strong donor-bound parameter to predict short-term graft performance.

8.3 Role of Prone Ventilation

Prone ventilation for 12-16 hours has been shown to improve oxygenation and increase utilization of the donor lungs in brain dead donors suffering from hypoxemia and atelectasis. This improvement in oxygenation is likely secondary to improvement in V/Q matching, better drainage of secretions, and long-lasting benefits in improving the atelectasis. Safe prone positioning does need expertise and more hands- on to prone the donors especially with the tubes and catheters in place. OPO agencies should coordinate with the hospitals/health care providers to educate the staff and the family on the importance of prone positioning. In an experimental controlled donation after circulatory death (cDCD) swine model, the prone ventilation strategy has demonstrated to improve alveolar air distribution, less edema and cell inflammation, and decrease cell death during warm ischemia time (WIT). As a result, lung function and quality were better during the ex vivo lung perfusion (EVLP) system compared to the supine group. Placing cDCD donors in a prone position following the declaration of death may increase the utilization of these lungs [66].

8.4 Fluid Management

Euvolemia is one of the most crucial objectives in the maintenance of donor organs. Most brain-dead organ donors run the risk of vascular tone loss, increased permeability of capillaries and intravascular volume depletion. The sympathetic surge just before brain death leads to hemodynamic alterations such as neurogenic hypertension followed by hypotension. Crystalloid solutions (0.9% sodium chloride or Ringer's lactate) are the best options for fluid replenishment and maintenance in donors with reduced preload [67, 68]. Patients with hypernatremia (serum Na^+ >145 mmol/liter) may be treated with dextrose-containing fluids or hypotonic solutions, such as 0.45% sodium chloride. In donors with metabolic acidosis, sodium bicarbonate may be used [69]. Maintaining euvolemia and adequate organ perfusion should be carefully balanced against development of pulmonary edema [70]. A PA catheter should be considered to correctly measure

filling pressures, vascular pressures and to monitor cardiac activity [71]. Moreover, sudden intravascular volume overloads may impair the right ventricular function and can result in renal dysfunction [68, 72, 73].

8.5 Inotrope and Vasopressor Use

Despite fluid resuscitation, around 90% of brain-dead donors experience persistent hypotension and need vasopressors [74, 75]. The recommended first-line medication, currently, is vasopressin (V1 and V2 receptor agonist) at the lowest dosage required [76, 77]. Its usage has been linked to enhanced donor heart function (perhaps by permitting the cessation of catecholamine support) and greater donor organ recovery [78, 79]. Dopamine could be an alternate first-line medication, especially for individuals who need inotropic assistance [69, 73]. The administration of low-dose dopamine (4 mg/kg/min) to donors already on norepinephrine at a rate of less than 0.4 mg/kg/min led to a decrease in the need for post-transplant dialysis in both recipients of renal and heart transplants from the same donor, according to a notable prospective, randomized-controlled trial [80]. Epinephrine and norepinephrine can also be used to achieve hemodynamic targets. But their use can downregulate the beta-receptors in the heart, thereby reducing post-transplant contractility [81]. Though norepinephrine usage in the donor has been deemed safe in recent studies, higher doses of these drugs (>0.2 mg/kg/min) have been observed to raise the likelihood of cardiac damage [82-84]. Echocardiograms should be evaluated considering that donors were on vasopressors at the time of the study and may have to be repeated.

8.6 Hormone Replacement Therapy

Following brain death there is often an abrupt fall in the serum level of hormones such as cortisol, insulin, antidiuretic hormone, and thyroxine. Hormonal therapy is crucial to ensure effective organ perfusion and function [85]. Administration of high-dose corticosteroids (15 mg/kg methylprednisolone) soon after brain death decreases the systemic inflammatory response, pro inflammatory cytokines and lung injury and has shown to improve oxygenation and increase the lung procurement rate, compared to controls [86]. Recent research indicates that even replacement with lower doses of steroids (300 mg of hydrocortisone) can improve oxygenation and hemodynamic stability while causing less hyperglycemia compared to large doses of methylprednisolone [87, 88]. The drop in anti-diuretic hormone coupled with reduction in sympathetic vascular tone after brain death, causes diabetes insipidus in 80% of donors which substantially increases the risk of hypotension, hemoconcentration and hypernatremia [89]. Donors should be monitored for polyuria (urine output >3 ml/kg/hour or 3 liters/day), high or rising serum osmolality, low or dropping urine osmolality and hypernatremia (serum Na^+ >145 mmol/liter) [76]. Vasopressin can be used to treat DI following brain death. Desmopressin administration in normotensive patients has been linked to enhanced donor organ procurement [90, 91]. Thyroid hormone replacement can improve the donor heart function [62]. Reduced left atrial pressure from improved left ventricular contractility will lessen the chance of pulmonary edema. However, a randomized controlled trial failed to show a positive effect of T3 on the donor lung [87]. Hyperglycemia is often seen in BDD donors, because of reduced insulin production, increased insulin resistance, gluconeogenesis, and with the use of corticosteroids and maintenance fluids that

contain dextrose [92]. It is recommended to target glucose concentration of 72 to 180 mg/dl (4-10 mmol/liter) [69, 73].

8.7 Antibiotics

The selection of antibiotics should be based on BALF microbiology studies including culture and drug sensitivity testing.

9. Intraoperative Assessment

Spinal reflexes may still be present in DBD donors, in which case a muscle relaxant may be necessary to inhibit somatic reactions to surgical stimulation [93]. When the abdominal procurement team separates the liver in situ before removal, the length of the donor operation might vary significantly. In the event of major bleeding, there may be large fluid changes and a blood transfusion may be necessary. Tidal volume should be kept at 6 to 8 ml/kg as part of a lung-protective ventilation strategy. Prior to donor lung retrieval, hemodynamic and metabolic goals should be kept intact [94, 95].

10. Pulmonary Vein Gas as A Tool for Assessing Donor Lungs

Arterial blood gas though a reliable indicator of oxygenation in peripheral tissues, PaO_2 in the donor as often measured from peripheral arterial access line may not always reflect the true oxygenation capacity of the donor's lungs. An arterial blood sample reflects gas exchange in both lungs and does not provide any information on each individual lung. Hence, pulmonary vein gas measurement from individual pulmonary vein blood gases allows for an accurate evaluation of gas exchange capacity of each lung lobe during the procurement process [96]. In one particular study, differential pulmonary vein gases were a better predictor of primary graft dysfunction following lung transplantation compared to measurements of arterial blood gases taken from the donor [97, 98].

The study by Costa et al proposed that the inclusion of selective pulmonary vein gases should be taken into account as an objective measurement to support the assessment of the donor surgeon. This additional source of evaluation provides a more accurate and objective means to assess the function of each individual lung, particularly in situations where there are uncertainties related to radiographic findings and marginal central challenge gases [99].

Intra-operative bronchoscopy should be diligently done to assess anatomical variants such as bronchus suis (an accessory bronchus arising from the supracarinal trachea and supplying the right upper lobe of the lung) as well as note intra-luminal irregularities like growths, airway inflammation, bleeding or quantify secretions. If the donor has a tracheostomy tube, switching it to an oral endotracheal tube (ETT) should be considered when feasible. In case of donors with small-sized ETT (<8.0 or 7.5), it should be upgraded prior to the start of the procedure to enable therapeutic bronchoscopy. Finally, as convention arterial blood gas should be drawn for analysis with FiO_2 at 100% and PEEP of 5.

11. Optimizing Uniform Distribution of Pulmoplegia

Atelectatic lung areas do not receive adequate perfusion. Paying close attention to pulmonary cannula placement is prudent especially during concomitant heart procurement. Inserting the cannula too distally results in preferential delivery of pulmoplegia into the left lung. Furthermore, the use of pressure bags for delivery should be avoided. Instead, the flush should be kept at 30 cm above the level of patient's head and allowed to run by gravity. Every precaution should be taken to avoid airlock. Adequate venting of the heart should be ascertained once pulmoplegia administration is initiated. High FiO_2 levels is deleterious to lung parenchyma and hence should be lowered to less than 50% during flushing and harvesting. A retrograde flush (with 250-500 mL per pulmonary vein) on back table is recommended to clear clots in pulmonary vasculature. This should be delivered by gravity alone without the use of pressure bags to avoid the development of pulmonary edema. When the heart is harvested concomitantly it is important to ensure an adequate pulmonary vein cuff. Donor pretreatment with prostaglandin E1 a pulmonary vasodilator has shown to provide excellent graft preservation.

12. Use of LungGuard

The Paragonix LUNGguard DLPS is a medical device approved by the FDA. It is designed to preserve donor lungs during transportation and transplantation using cold storage solutions. If donor lungs have been preserved for longer than the accepted time, the transplant surgeon should assess their suitability for transplantation based on clinical guidelines and the best interests of the recipient. The LUNGguard DLPS enabled the safe transportation of donor lungs over a distance of approximately 7,705 kilometers, even with a total ischemia duration exceeding 13 hours [100]. The GUARDIAN-LUNG study is an ongoing registry study conducted in the U.S. and Europe. Its primary objective is to evaluate short-term (within 48 hours), intermediate-term (3- and 6-month follow-up), and long-term (1-year follow-up) outcomes of lung transplant patients. Standard protocols for lung transplantation remained unchanged during the study. The study aims to collect and evaluate various clinical effectiveness measures in patients who received donor lungs preserved and transported using the Paragonix LUNGguard DLPS. It also examines the impact of donor, recipient, and transport-related factors on patient outcomes, such as donor clinical backgrounds, total ischemic times, and recipient factors. The study is currently gathering retrospective data from medical records of previously transplanted patients and new patients who meet the eligibility criteria. The primary outcome measures include the incidence of Primary Graft Dysfunction (PGD), rejection rates, survival duration after transplantation, length of stay in the ICU, and length of hospital stay. Secondary outcome measures include the number of re-hospitalizations and the duration of mechanical support required by the patients [101].

13. Donor Lung Weight Measurement

The build-up of fluid in the alveolar and interstitial space is known as extravascular lung water (EVLW). EVLW during EVLP causes elevated lung weight, which is a common sign of ischemia reperfusion injury (IRI) and may be linked to impaired lung function [102]. In a recent study, Okamoto et al found that when lung weight was corrected for body size, bigger lungs had worse early clinical outcomes in both EVLP and straight lung transplant patients [103]. In an isolated

perfused rat lung model, Motoyama et al. revealed that damaged lungs following warm ischemia showed considerable lung weight increase after 20 to 60 minutes of perfusion compared with non-injured lungs [104, 105]. Real-time lung weight measurements were used by Sakanoue et al. to identify EVLW in clinical acellular EVLP. According to the study, lung weight rise at 10 to 60 minutes can be a good indicator of transplant suitability [106].

In a recent study, the researchers simulated the perfusion of porcine lungs to mimic the variety of injuries that can occur in donor lungs. They aimed to evaluate the usefulness of real-time lung weight measurements during ex vivo lung perfusion (EVLP) in assessing lung injury and determining the suitability of donor lungs for transplantation. The researchers used 15 porcine lungs with different degrees of warm ischemia. The lungs were perfused using the Lund protocol [107, 108]. The researchers measured various parameters during the EVLP, including pulmonary artery pressure, filtration coefficient (Kfc), and transpulmonary blood flow (Qf). They found that increased Kfc values were associated with an increase in real-time lung weight gain, indicating fluid leakage. They also observed that abnormal lung weight gain at 40 minutes into the EVLP could serve as a warning for further assessments at 1 and 2 hours.

The researchers divided the real-time lung weight gain into three phases:

I. The initial rewarming phase,
II. The evaluation phase, and
III. The recondition phase.

They found that the normalized lung weight gain was greater in the evaluation phase than in the reconditioning phase, and it was highest during evaluation when the FiO_2 was 1.0. This implies that increased tidal volume (TV) during recruitment can lead to increased fluid leakage [109].

The study suggests that real-time lung weight measurements can be useful in assessing lung injury and determining the suitability of donor lungs during EVLP. Abnormal lung weight gain at 40 minutes can serve as an early warning sign, and lung weight data can help guide therapeutic interventions, such as hemoconcentration. The study also highlights the potential of real-time lung weight measurements in identifying procedural problems during EVLP [109].

During transport, lungs are left inflated at only 75-80% of their total capacity and at a FiO_2 of 50%. Doing so reduces the chances of primary graft dysfunction. Modern air transport in high-altitude flights has unavoidable atmospheric pressure drops which lead to volume expansion of the lung air. This can happen despite pressurization of aircraft cabins; thus inflation of lungs only up to 75-80% of total capacity is crucial to avoid barotrauma [110].

14. Effect of Local Anaesthetics on Lung Ischemia Reperfusion Injury

Lung ischemia-reperfusion injury (LIRI) is a complex process involving various factors like pulmonary endothelial cells, alveolar epithelial cells, alveolar macrophages, neutrophils, mast cells, platelets, proinflammatory cytokines, and surfactant. Consequently, evaluating the protective effects of volatile anesthetics in LIRI is challenging [111]. Nonetheless, several studies conducted on animals have shown that administering isoflurane and sevoflurane prior to ischemia can have beneficial effects in reducing injury caused by reperfusion in rat lungs [112]. This positive outcome is attributed to the anti-inflammatory impact on immune cells and the anti-apoptotic effect on lung tissue. Sevoflurane may also inhibit the recruitment of polymorphonuclear neutrophils into the lung [113]. Additionally, the observed protective effect could be a result of changes in vascular smooth

muscle tone, as volatile anesthetics are effective pulmonary vasodilators. Other potential explanations for the protective effects of isoflurane and sevoflurane on ischemia-reperfusion (IR)-induced lung injury include the suppression of metabolism or reduced use of adenosine triphosphate (ATP), as well as the activation of potassium adenosine triphosphate channels [114].

15. Ex Vivo Lung Perfusion (EVLP)

EVLP, has now become an established tool, to assess and rehabilitate donor lungs outside the body after procurement and prior to implantation to optimize the marginal lungs or high-risk donors that would otherwise be considered unsuitable for lung transplantation [115]. This approach was first used by Steen in a DCD donor and its effectiveness prompted several investigators all over the world [115-122]. Several studies have demonstrated comparable outcomes on utilization of such lungs after EVLP compared to conventional methods. They have demonstrated to increase donor lung utilization rates, decrease waiting times, and improve patient outcomes.

While on EVLP, multiple testing including radiography, bronchoscopy, angioscopy and treatment modalities can be performed. Another testing modality which can be done is lung ultrasound to assess the degree of edema in the lungs while on EVLP, as demonstrated in the "CLUE" (direCt Lung Ultra-sound Evaluation) study. Ultrasound images are taken of the donor lungs and the percentage of B-lines (which represent extravascular lung water) determined and quantitative assessment of the extravascular lung water is done. In the study by Ayyat et al, 45 lungs from 23 donors were assessed as part of a clinical EVLP program and noted to have had considerably lower CLUE values than the lungs unsuitable for transplantation [123]. Overall, the CLUE methodology further enhances the evaluation of donor lungs during EVLP by offering a non-invasive and simple method. Future work is geared towards building portable and automated EVLP equipment as well as improving the assessment and management of donor lungs utilizing enhanced imaging and immunologic or genetic analysis.

16. Interventional Cross-circulation Platform

Another method of rehabilitating donor lungs is by using cross-circulation to provide prolonged, systemically regulated normothermic extracorporeal organ support. Guenthart et al, describe their results in swine model of donor lungs unsuitable for transplantation and demonstrated that (i) lungs could be maintained on cross-circulation support without decline in lung function or tissue integrity, (ii) were amenable to repeated therapeutic interventions, and (iii) displayed evidence of cellular regeneration and improved function over the course of 36 hours [124].

17. Artificial Intelligence in Organ Transplantation

Recent advancements in technology have made possible to assist medical professionals in making decisions which directly impact donor organ allocation and patient survival. The uniqueness of each organ and the patients' heterogeneous responses pose unique challenge that can be overcome by the utilization of artificial intelligence (AI) and machine learning (ML).

Organ individualized treatment effect (ITE) – is a prediction-based model made up of two components: a high-dimensional ITE estimator and an organ-to-patient policy. It assigns organs to patients based not only on its own estimates of the potential outcomes but also on organ scarcity.

By modelling and accounting for the arrival of new organs, the total life years across the population are significantly increased [125]. Organ sync, another novel decision support system for organ allocation developed in Cambridge, UK, is a queuing-theoretic framework which clusters the organs into "organ types", and then construct priority queues (associated with each organ type) wherein incoming patients are assigned. It facilitates the trade-off between patient waiting time and anticipated survival time by grouping the organs into organ families [126]. One patient is added to the transplant waiting list in the US every nine minutes (organ procurement and transplantation network (OPTN), 2021b). As the demand rises for organs, advancements like these including AI are the need of time.

18. Conclusion

Lung transplantation remains challenging among all the solid organ transplants. With the invent of new therapies and interventions for various lung diseases and the rising population of advanced age does necessitate the implementation of strategies to screen and utilize the donor lungs at a higher rate to decrease the waitlist mortality and to improve the patient survival. There is continued need for advancement in donor lung evaluation, preservation, and transportation techniques and consensus among OPO's, donor centers and the transplant centers to increase the donor utilization rates.

Abbreviations

AI	artificial intelligence
BDD	brain dead donors
CDC	center for disease control
CF	cystic fibrosis
CVP	central venous pressure
DCD	donation after circulatory death
EVLW	extravascular lung water
EVLP	ex vivo lung perfusion
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
IPF	idiopathic pulmonary fibrosis
ISHLT	International society for heart and lung transplantation
LTP	lung transplant programs
LTx	lung transplantation
ML	machine learning
OPTN	organ procurement and transplantation network
PGD	primary graft dysfunction
pTLC	predicted total lung capacity
PH	pulmonary hypertension

Author Contributions

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Competing Interests

The authors have declared that no competing interests exist.

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