Novel Approaches to Expanding the Lung Donor Pool: Donation After Cardiac Death and Ex Vivo Conditioning

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Lung transplantation (LTx) represents a unique lifesaving therapy for patients suffering from end-stage lung disease. Ever since the world’s first successful lung transplant was performed in Toronto 27 years ago, listing of patients in need of LTx has been constantly increasing, but the number of organ donors has remained mostly static. This donor shortage is further aggravated by very low use rates of donor lungs (~15%) from multiorgan donors due to the conservative practices of many transplant groups. Recently, two novel approaches have been developed to potentially increase the availability of donor lungs. In the first approach, lungs from donation after cardiac death (DCD) donors are used to increase the quantity of organ donors. In the second approach, a newly developed normothermic ex vivo lung perfusion (EVLP) technique is used as a means of reassessing the adequacy of lung function from DCD and brain death donors, and potentially optimizing function of injured donor lungs initially unsuitable for transplantation. This review discusses both of these novel approaches in detail.

LUNG DONATION AFTER CARDIAC DEATH

Organs have traditionally been harvested only from individuals who have died after meeting criteria for brain death (ie, donation after brain death [DBD] donors). However, to help overcome the organ donor shortage, some programs have initiated the use of DCD donors. At the First International Workshop on DCD held in Maastricht in the Netherlands in 1995, 4 types of donors were defined: Categories I (dead on arrival) and II (unsuccessful resuscitation) comprise the uncontrolled donors. Categories III (awaiting cardiac arrest) and IV (cardiac arrest in brain-dead donors) include the controlled donors (Table 1). The principal steps in the sequence of care in controlled and uncontrolled DCD donation are shown in...

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- Lung donation after cardiac death
- Ex vivo lung perfusion
- Pharmacologic/molecular intervention

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Controlled DCD donation is the most accepted type of DCD donation to date for lungs, liver, and kidneys. Controlled DCD includes patients who have a dismal prognosis, but whose condition does not fulfill the strict definition of brain death. Supportive care that is thought to be futile is usually withdrawn from these patients at a planned time; this subsequently leads to patient death, at which time organ retrieval can proceed. The DCD donor pool is becoming substantial; from 2006 to 2008, there was an increase of 24% in the DCD category compared with a 2% decrease in the number of consented DBD donors. By far the largest percentage increase in multiorgan donors in recent years has been in the DCD category, and this will significantly affect organ use in the future.

**Experimental Research with Lung DCD**

The lung is a unique organ in that it is not dependent on blood perfusion for aerobic metabolism but instead can use a mechanism of passive diffusion through the alveoli for oxygen delivery. The initial experimental studies performed in dogs by Egan and colleagues demonstrated the feasibility of transplanting donor lungs after cardiocirculatory arrest. Lungs that were retrieved 1 hour after arrest could sustain life after transplantation; however, most recipient animals died when lungs that were retrieved 4 hours after arrest were transplanted. This group further demonstrated the importance of lung inflation and intra-alveolar oxygen concentration in a DCD setting. In unventilated animals, 77% of lung cells were nonviable 12 hours after death, which was comparable to results from nitrogen-ventilated cadaver lungs. Oxygen-ventilated cadaver rats, however, had only 26% nonviable lung cells. Moreover, the degree of ultrastructural damage observed in the oxygen ventilated group at 2 and 4 hours postmortem was not significantly different from that of normal controls. Thus, mechanical ventilation with oxygen after death preserved the lung ultrastructure and delayed cell death. Additional studies by Van Raemdonck and colleagues demonstrated that lung inflation post mortem was critical to the preservation of lung barrier functions and that inflation with room air ($\text{FiO}_2$ 21%) was equivalent to inflation with 100% $\text{FiO}_2$.

![Fig. 1. Overview of sequence of care in controlled and uncontrolled donation after cardiocirculatory death.](image-url)
Buchanan and colleagues\(^8\) showed excellent gas exchange 1 week after the transplantation of lungs that were retrieved by DCD protocol 30 minutes after death in a porcine model. Greco and colleagues\(^9\) showed similar gas-exchange characteristics of lungs from ventilated DCD pigs retrieved 30, 60, or 90 minutes after circulatory arrest compared with lungs retrieved from conventional donors. These studies supported the hypothesis that LTx from DCD donors may be feasible. Other studies were performed to determine the maximum tolerable warm ischemic time (WIT; time from arrest to cold flush) in DCD models, and 60 to 90 minutes seemed to be the acceptable limit for WIT.\(^7,10,11\) Topical cooling by circulating cold preservation solution in the pleural cavity through large-bore chest tubes has also been proposed as a method to better preserve lungs in an uncontrolled DCD situation during transportation of the donor to the hospital and the period of time required to obtain consent for donation.\(^12,13\)

Most of the experimental DCD studies have been performed using sudden cardiac arrest by drug administration or myocardial fibrillation. Therefore, this may not well represent the clinical scenario where a period of cardiopulmonary instability (also called the “agonal period”) occurs before circulatory arrest. Concerns have been raised about the injury that may occur to the pulmonary allograft during this phase. This injury might in fact be more crucial than the postmortem insult that occurs during the warm ischemic interval and preservation process. Neutrophils can be activated and sequestrated into the lung during this time, and release proinflammatory mediators that can injure the lungs before retrieval. Tremblay and coworkers\(^14\) investigated the impact of premortem hypotension and cardiac instability in the setting of uncontrolled DCD (traumatic blood loss, myocardial infarction). In an isolated rat lung reperfusion model, graft function was severely impaired in rats that underwent 1 hour of hemorrhagic shock by exsanguination followed by 2 to 3 hours of in situ ischemia. Another recent study demonstrated that the premortem agonal phase in DCD induces a sympathetic storm leading to capillary leak with pulmonary edema and reduced oxygenation on reperfusion. Graft quality was inferior in DCD lungs when recovered from a hypoxic cardiac arrest model in comparison with uncontrolled exsanguination or fibrillation setting.\(^15\) Because the airway is unprotected, aspiration of gastric contents can occur during the agonal phase in a DCD donor, adding additional lung injury.

There are, however, theoretical advantages of DCD lung donation. The use of DCD organs can avoid brain death–induced lung injury. Given the low use rates of lungs today, the lung appears to be vulnerable to the effects of brain death. Neurogenic pulmonary edema is a common injury in brain-dead donors and although the mechanism is not completely clear, it is thought that the sudden and profound increase in systemic vascular resistance generated by the catecholamine storm leads to a decrease in left ventricular output and an increase in left atrial (LA) and pulmonary capillary pressure. This increased pressure can cause injury to the pulmonary epithelium and, as a result, pulmonary edema forms by both hydrostatic and increased permeability mechanisms.\(^16\) Lung injury can also occur as a result of systemic inflammation following brain death. Increased circulating proinflammatory cytokines can result in the induction of cell adhesion molecules on pulmonary endothelial and epithelial surfaces.\(^17\) This process leads to the recruitment of neutrophils and monocytes to the lung, causing inflammatory lung injury. The authors have previously shown that interleukin (IL)-8 levels in donor lung tissue before and after transplantation increased with time after reperfusion, and that patients who developed severe primary graft dysfunction had significantly higher IL-8 levels during ischemia and after reperfusion.\(^18,19\) Similarly, Fisher and colleagues\(^20\) studied the levels of IL-8 in bronchoalveolar lavage (BAL) fluid from 26 donor lungs used for transplantation, and showed that a high concentration of IL-8 in donor BAL fluid was correlated with severe graft dysfunction and with early postoperative deaths. To further study the role of proinflammatory cytokines, the authors used real-time polymerase chain reaction (RT-PCR) to study the levels of IL-6, IL-1β, IL-8, IL-10, interferon-γ, and tumor necrosis factor α in the donor lung at the end of cold ischemia, and found that the IL-6/IL-10 ratio was predictive of recipient 30-day mortality.\(^21\)

The authors’ group in Toronto recently compared inflammatory mediators in DCD and DBD donors using lung tissue biopsies from human donor lungs used for transplantation. Lungs from DCD donors showed decreased proinflammatory cytokine profiles compared with DBD lungs. In particular, levels of IL-6 and IL-8 were significantly lower in DCD lungs.\(^22\) Moreover, in unsupervised clustering analysis of microarray data, DCD and DBD lungs generated distinct transcriptomic signatures and the two lung types differed most in pathways related to inflammation, such as nuclear factor κB. The gene sets enriched in DBD mapped to innate immunity, intracellular signaling, cytokine interaction, cell communication, and apoptosis pathways.\(^22\) These observations support the
concept that brain death results in the development of a systemic inflammatory response that can damage organs, with a deleterious impact on their function after transplantation.23–25

Clinical Experience with Lung DCD

The first LTx in humans was performed by James Hardy in 1963 using a lung from a DCD donor who died of a myocardial infarction. At that time, use of DCD was a necessity, as the concept of brain death was not yet legally established. Once brain death had reached general acceptance in the 1970s, all organs were harvested from DBD donors.

Uncontrolled donation

Apart from a case reported by Steen and colleagues26 in 2001 of a DCD LTx using a donor who died of myocardial infarct in hospital (Category I), the only experience with uncontrolled DCD LTx is from the group in Madrid, who described 17 cases.27,28 Lungs were retrieved from donors who suddenly collapsed outside the hospital (Category II). Cardiopulmonary resuscitation was started in the patient if sudden death from cardiac, neurologic, or traumatic origin occurred no longer than 15 minutes after arrival of the medical team. If these resuscitation maneuvers were not successful after more than 30 minutes, the potential donor was transported to the hospital where death was certified after cardiac massage was interrupted. Judicial and family permission for organ donation were then obtained. The cadaver was transported to the operating room and connected via the femoral vessels to an extracorporeal bypass machine with deep hypothermia and oxygenation for preservation of the abdominal organs. Both lungs were further cooled topically with 4 L of Perfadex solution at 4°C via 2 chest drains on each side. Oxygenation capacity was assessed in situ after sternotomy with a single pulmonary flush of 300 mL of venous donor blood mixed with Perfadex. An additional retrograde flush was administered on the back table after lung extraction with 250 mL Perfadex in each vein. Grade 2 or 3 primary graft dysfunction (PGD)29 occurred in 53% of the cases. Hospital mortality rate was 17%. The survival rates were 82% at 3 months, 69%, at 1 year, and 58% at 3 years. Although PGD and mortality rates were higher than expected after conventional LTx, the investigators argued that this source of organs is valid and justifiable in the context of severe organ shortage.

Controlled donation

Controlled (Categories III and IV) DCD LTx is by far the most accepted and used DCD type for donation. In 1995, Love and colleagues30 reported the first successful experience using a DCD lung donor. Since then, other groups slowly started to incorporate DCD transplantation into their programs, but it was not until the current decade that LTx from DCD became more widely accepted. Uncertainty about outcomes using DCD donor lungs has led transplant teams to be very conservative in organ selection when using this donor group. Whereas an average of 3.6 organs is transplanted from DBD donors, in DCD the average is 2.0.3 About 100 cases of DCD LTx have been reported to date. Table 2 summarizes the outcomes of DCD LTx from series where 10 or more cases have been reported. In contrast to

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Category</th>
<th>PGD 2 or 3</th>
<th>BOS</th>
<th>Survival (Discharge, Discharge 1 y, 3 y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Antonio et al,28</td>
<td>17</td>
<td>II</td>
<td>53%</td>
<td>7% 1 y, 11% 2 y, 50% 3 y</td>
<td>82%, 69%, 58%</td>
</tr>
<tr>
<td>Snell et al,37</td>
<td>11</td>
<td>III</td>
<td>18%</td>
<td>9%</td>
<td>100%, NR, NR</td>
</tr>
<tr>
<td>Mason et al (UNOS),35,36</td>
<td>36</td>
<td>III</td>
<td>NR</td>
<td>NR</td>
<td>NR, 94%, NR</td>
</tr>
<tr>
<td>Cypel et al,33,68</td>
<td>10</td>
<td>III–IV</td>
<td>40%</td>
<td>None</td>
<td>100%, NR, NR</td>
</tr>
<tr>
<td>Puri et al,34</td>
<td>11</td>
<td>III</td>
<td>36%</td>
<td>27%</td>
<td>82%, 82%, NR</td>
</tr>
<tr>
<td>De Oliveira et al,31</td>
<td>18</td>
<td>III</td>
<td>33.3%</td>
<td>19.6% 1 y, 19.6% 3 y, 27.7% 5 y</td>
<td>94%, 88.1%, 81.9%</td>
</tr>
<tr>
<td>Erasmus et al,38</td>
<td>21</td>
<td>III</td>
<td>23.8%</td>
<td>14.2%</td>
<td>95.2%, 95.2%, 90.4%</td>
</tr>
</tbody>
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Abbreviations: BOS, bronchiolitis obliterans syndrome; NR, not recorded; PGD, primary graft dysfunction grade; UNOS, United Network for Organ Sharing.

Series reporting 10 or more cases are included in this table.
uncontrolled DCD, early and intermediate outcomes of transplantation of Category III DCDs have been comparable to LTx using DBD. Only one recent report has shown increased rates of severe PGD (36%) and higher 30-day (18%) and 18-month (36%) mortality. A recent review of the United States experience using data retrospectively collected from the UNOS (United Network for Organ Sharing) database demonstrated an overall survival after LTx at 1, 12, and 24 months of 94%, 94%, and 87%, respectively, for recipients receiving lungs from DCD donors, compared with 92%, 78%, and 69%, respectively, from DBD donors. The largest single-center experience comprising 21 cases of controlled DCD LTx was reported by Erasmus and colleagues with an excellent 1-year survival of 95%. Although the DCD statistics are highly favorable, the small sample size in these studies does not allow for a definitive conclusion as to whether DCD provides better early and intermediate outcomes compared with DBD. Transplant teams have been highly selective in donor and recipient selection for DCD procedures, which may have favorably influenced the outcomes.

A better understanding of how the DCD process affects donor lungs will have a major impact in expanding the use of DCD organs and alleviating the organ shortage. The time between withdrawal of life support therapies (WLST) and cold flush in DCD lungs is a period of risk for lung injury. Once WLST is initiated, the lung is at increased risk from events such as hypotension, warm ischemia (once systolic blood pressure is <50 mm Hg or after cardiac arrest), and aspiration. Two small series have shown an inverse relationship between this “agonal” time and $\text{PaO}_2/\text{FiO}_2$ ratios after transplantation, but firm conclusions await performance of larger studies.

DCD Donor Lung Evaluation and Procedure

DCD donor lung evaluation is in general similar to DBD and includes medical history, arterial blood gases, chest radiograph findings, bronchoscopy findings, and direct examination of the lungs in the operating room. Of importance, decisions about WLST, management of the dying process, and the determination of death by cardiocirculatory criteria must be independent of the donation/transplant processes. Whether WLST should occur in the intensive care unit (ICU) or in the operating room should be based on family preferences, institutional logistics, resources, and facilities.

In most protocols, the donor receives heparin (30,000 IU) 30 minutes before WLST, although successful clinical DCD transplantation has been performed without donor heparinization. When cardiac arrest occurs, death is certified by 2 physicians from the donor hospital ICU team after a 5- to 10-minute period of absent palpable pulses, blood pressure, and respiration. The donor is then quickly reintubated, generally by one of the LTx team members. A flexible bronchoscopy is then performed to rule out aspiration of gastric contents during cardiac arrest, presence of mucopurulent secretions, or anatomic abnormalities. Concurrent with the bronchoscopy, another member of the team performs a median sternotomy and cannulation of the pulmonary artery (PA), followed by the standard procurement technique. Because there is insufficient time for careful examination of the lungs before cold flush perfusion, the decision to use the lungs for LTx and initiate recipient anesthesia is in general made only after the lungs are explanted and careful macroscopic evaluation is performed. Functional reassessment of these organs using EVLP is very useful and has become routine in some centers (see section on EVLP).

Ethical Considerations

DCD organ donation raises several very important ethical considerations. Although it is generally seen as appropriate to use the human body as a source of tissues and organs to serve the well-being of other individuals, the donor’s body should always be treated with great care and respect. The care of the dying patient must never be compromised by the desire to protect organs for donation or to expedite death to allow timely organ retrieval. The first responsibility of health care providers, regardless of the potential for donation, is to advance the well-being of the dying patient, including psychological, emotional, and spiritual well-being in addition to physical well-being. Decisions about care at the end of life should be based on the known values and beliefs of the patient. These decisions should be consistent with what each patient understands to be a meaningful life and death, including the ability or desire to provide organs to others. Support for families and loved ones should continue through all phases of dying: before, during, and after WLST.

It is important to recognize and minimize conflicts of interest that might occur in the setting of DCD. Conflicts of interest occur when those involved in providing health care have relationships with people or organizations outside the healing relationship that may influence their actions, regardless of whether they believe these relationships actually affect their judgment. Failure to identify and disclose such conflicts may
EX VIVO LUNG PERFUSION

Rationale and Experimental Work to Date

Another novel strategy to help overcome the shortage of donor lungs is the reassessment and conditioning of injured donor lungs using normothermic EVLP. The current clinical practice of lung preservation is that of cold static preservation (CSP). During retrieval, a cold pulmonary flush using low potassium dextran preservation solution (Perfadex; Virolife, Göteborg, Sweden) is coupled with topical cooling and lung ventilation. Thereafter, the lungs are transported at 4°C in an inflated state. Hypothermia reduces metabolic activity to the point that cell viability can be maintained in the face of ischemia (5% of metabolic rate at 37°C). Cold temperature preservation continues to be an important component of lung preservation.

Physiologic normothermic (37°C) or near-normothermic (25–34°C) ex vivo perfusion has become a popular research tool as a preservation alternative in experimental models of lung, liver, and kidney transplantation. One important advantage of normothermic perfusion is the allowance of functional reassessment during the ex vivo phase of organ preservation. EVLP likely provides a more accurate assessment of lung function compared with in vivo assessment because: (1) it provides an excellent environment for recruitment and reexpansion of atelectatic lung areas; (2) it allows for effective clearance of bronchial secretions; (3) it allows for removal of clots in the pulmonary circulation through the use of transient retrograde perfusion at the beginning of the procedure; (4) it allows for all ventilator volumes and pressures to be transferred directly to the lungs without interference of the chest wall and diaphragm; and (5) the dextran in the perfusate solution facilitates perfusion of the pulmonary microvasculature.

Another theoretical advantage of normothermic perfusion is the maintenance of normal metabolism, permitting restoration of normal functions (using organ innate reparative mechanisms or through active therapeutic interventions). Maintenance of organs under physiologic temperatures is not a novel concept. Carrel and Lindbergh described the concept of the “culture of whole organs” in 1935. However, until recently, isolated lung perfusion has been used only to study basic lung physiology, usually in small animal lungs. In general, experimental work in isolated lung perfusion systems has shown that this leads to progressive deterioration of lung function. The resurgence of EVLP as a potentially important tool in lung transplantation started with the work of Steen and colleagues. Envisioning the use of EVLP as a method to reassess lungs from uncontrolled DCD donors (since these organs cannot be evaluated in vivo), this group described an ex vivo perfusion system and made an important contribution by developing a specific solution (Steen solution) that allows for ex vivo perfusion of the lungs without development of pulmonary edema. After a short period (60–90 minutes) of ex vivo evaluation, they demonstrated that the lung could be successfully transplanted in large animals and described its use in a case report of human LTx.

Following these publications, other groups demonstrated the feasibility of short-term EVLP using the technique described by Steen to evaluate lung function in animal models of DCD and experimentally using injured human lungs rejected for transplantation. Erasmus and colleagues extended the EVLP duration to 6 hours. Although feasible, circuit-induced impairment of lung function, as evidenced by increased pulmonary vascular resistance and increased airway pressures, became apparent toward the end of the procedure.

The Toronto group modified the EVLP system and strategy in order to be able to maintain lungs in the EVLP system for at least 12 hours without additional injury. The use of an acellular perfusate, a closed circuit with protective low perfusion pressure and stable positive LA pressure (5 mm Hg), and a protective mode of mechanical ventilation (tidal volume of 7 mL/kg, rate of 7 breaths per minute, with a positive end-expiratory airway pressure of 5 cm H2O) were critical modifications to achieve 12 hours of perfusion stability. In the authors’ initial studies using normal pig lungs, stable lung function during 12 hours of EVLP was demonstrated. This stability during prolonged normothermic EVLP translated into excellent post-transplant lung function (\(\text{PaO}_2/\text{FiO}_2 = 527 \pm 22 \text{ mm Hg}\)), low edema formation, and preserved lung histology after transplantation. The acellular perfusion assessment of lung function accurately correlated with posttransplant graft function and the addition of red blood cells did not provide additional functional information compared with acellular perfusate. This study provided the proof of concept that EVLP is able to maintain donor lungs for a prolonged period of time without damaging the organ. The authors further examined the impact of prolonged EVLP on ischemic injury. Pig donor lungs were cold-preserved for 12 hours and subsequently divided into two groups: CSP or
normothermic EVLP for an additional 12 hours (total 24 hours preservation). EVLP preservation resulted in significantly better lung oxygenation and lower edema formation rates after transplantation when compared with CSP. Alveolar epithelial cell tight junction integrity, evaluated by zona occludens–1 protein staining, was disrupted in the cell membranes after prolonged CSP but not after EVLP. Integrity of functional metabolic pathways during normothermic perfusion was confirmed by effective adenoviral GFP gene transfer and transgene expression by lung alveolar cells.

**Technique for EVLP**

The authors have previously described the details for their acellular lung protective EVLP technique, including a detailed discussion about the rationale for the chosen ventilatory and perfusion strategies. The components of the circuit are shown in Fig. 2 and the EVLP strategy is shown in Table 3. The lungs are transferred from the back table to the XVIVO chamber (Vitrolife) placed on a second draped sterile operating room back table. First, the LA cannula is connected to the circuit and a slow retrograde flow (using the circuit bridge) is performed to de-air the PA cannula. Once de-airing is complete, the PA cannula is connected to the circuit and anterograde flow is initiated at 150 mL/min with the perfusate at room temperature. The temperature of the perfusate is then gradually increased to 37°C over the next 30 minutes. Before increasing flow beyond this level, a careful check of the system is made. The PA and LA pressure readings are double checked. When a temperature of 32°C is reached (usually over 20 minutes), ventilation is started and the perfusate flow rate is gradually increased to the target flow (40% of estimated donor cardiac output) within 60 minutes. Once ventilation is started, the flow of gas (86% N₂, 6% O₂, 8% CO₂, Praxair) that will deoxygenate and provide carbon dioxide to the inflow perfusate via the gas exchange membrane is initiated (started at 0.8 L/min) and titrated to maintain inflow perfusate PCO₂ between 35 and 45 mm Hg.

**Ex vivo Lung Perfusion Equipment**

![Diagram of ex vivo lung perfusion circuit](image)

- **Gas for deoxygenation**: 86% N₂, 8% CO₂, 6% O₂
- **Red**: Venous (Oxygenated) perfusate
- **Blue**: Arterial (Deoxygenated) perfusate
- **Perfusate**: Acellular Steen

Fig. 2. Components of ex vivo lung perfusion circuit. The perfusate is circulated by a centrifugal pump passing through a membrane gas exchanger and a leukocyte-depletion filter before entering the lung block through the pulmonary artery. A filtered gas line for the gas-exchange membrane is connected to an H-size tank with a specialty gas mixture of oxygen (6%), carbon dioxide (8%), and nitrogen (86%). A heat exchanger is connected to the membrane gas exchanger to maintain the perfusate at temperature. Pulmonary artery flow is controlled by the centrifugal pump and measured using an electromagnetic flow meter. The outflow oxygenated perfusate returns through the left atrial cannula to a hard-shell reservoir. Lungs are ventilated with a standard ICU-type ventilator. The lungs are contained in a specifically designed lung enclosure (XVIVO; Vitrolife, Göteborg, Sweden).
Pharmacologic Interventions During EVLP

EVLP offers an ideal environment for therapeutic interventions to optimize the donor lung prior to transplantation. The system provides the opportunity to better select which lungs to treat and then to reevaluate to confirm a positive treatment effect. Furthermore, side effects of the treatment are greatly minimized by the targeted treatment of the organ, and inflammatory responses in the repair process can theoretically be decreased, due to the absence of circulating immune cells. Lastly, EVLP provides flexible timing for treatment in contrast to in vivo treatment of the donor, for which the time available for interventions is limited.

Several pharmacologic investigations have been explored experimentally using EVLP as a platform. Agents to remove pulmonary edema by enhancing alveolar fluid clearance have been studied. Sakuma and colleagues demonstrated the role of epinephrine in enhancing alveolar fluid clearance and removing pulmonary edema. Treated lungs demonstrated an alveolar fluid clearance of 84% above control clearance. The same group demonstrated the role of β-adrenergic stimulation in clearance of pulmonary edema using a human EVLP model. Because many donor lungs rejected for transplantation because of poor function have unrecognized pulmonary embolism, Inci and colleagues proposed the use of fibrinolytics during EVLP. This strategy might be especially important in DCD donors in whom donor heparinization might not be possible. Adding urokinase to the perfusate during EVLP resulted in improved graft function by reducing pulmonary vascular resistance and increasing oxygenation after 3 hours of warm ischemia. The same group demonstrated that intra-airway surfactant administration during EVLP improved donor lungs injured with acid aspiration. A large number of donor lungs are declined because of infection acquired during critical illness and brain death. EVLP provides a very attractive platform for administration of high doses of antimicrobials without the risk of injuring other organs. In addition, the half-life of these drugs is significantly prolonged in the system. One recent study showed that antibiotics decreased the bacterial load, but further investigations are required to prove this very promising concept.

Molecular Interventions During EVLP

Another exciting method of lung repair is gene therapy. Gene therapy in LTx is attractive because transtracheal delivery of gene vectors can localize the effect to the lung graft. Although ex vivo vector delivery is an attractive concept, ex vivo gene transfer techniques have been traditionally ineffective in organ transplantation because of inhibition of metabolism during hypothermic preservation. However, with normothermic EVLP, the authors have demonstrated efficient gene transfer in alveolar epithelial cells and macrophages 12 hours after ex vivo gene delivery. Using injured human donor lungs rejected for transplantation, the authors showed that ex vivo adenoviral-mediated IL-10 (a potent anti-inflammatory cytokine) gene delivery at the start of 12 hours of EVLP significantly improved lung function, reduced inflammation (down-regulation of proinflammatory cytokines), and promoted cytoskeletal structural lung repair.

Clinical Experience with EVLP

The first clinical use of an EVLP system was described by Steen and colleagues in 2001 to briefly assess lung function in an organ harvested from a DCD donor. The same group reported their experience with 60 to 90 minutes of blood-based perfusion to assess 6 high-risk donor lungs before transplantation. Although outcomes were considered acceptable, the postoperative length of stay...
in the ICU was longer in recipients of perfused lungs as compared with conventional transplantation (13 vs 7 days).79,80

The first prospective clinical trial using EVLP was recently completed at the University of Toronto, and the results have been presented at the annual meeting of the International Society of Heart and Lung Transplantation.81 In this study, 23 lung transplants were performed after 4 hours of EVLP using the acellular protective ventilation/perfusion strategy developed by the authors’ group.67,68 This trial demonstrated that extended normothermic EVLP is safe for the assessment of high-risk donor lungs, and similar early outcomes were obtained in a comparison with conventionally selected and transplanted donor lungs.

SUMMARY

Lung transplantation using DCD donors is now a clinical reality, and outcomes from controlled donation have been comparable to brain death donors. Although the hemodynamic instability prior to death can injure the lung in DCD, the avoidance of the cytokine storm associated with brain death is a potential advantage in these organs, and some preliminary clinical studies have shown that inflammatory profiles are more favorable in lungs from DCDs when compared with DBDs.

By mimicking the lung’s natural physiologic environment and by providing oxygen and other substrates necessary for active metabolism, normothermic EVLP may offer the next step in lung assessment and preservation. Treatment of donor lungs prior to transplantation, such as with pharmacologic agents to reduce pulmonary edema and inflammation or gene therapy to better prepare the organ to deal with the reperfusion and subsequent immunologic insults, will be the major goals of the future.

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