Feasibility of Lung Transplantation From Donation After Circulatory Death Donors Following Portable Ex Vivo Lung Perfusion: A Pilot Study

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ABSTRACT

Background. Donation after circulatory death (DCD) has the potential to significantly alleviate the shortage of transplantable lungs. We report our initial experience with the use of portable ex vivo lung perfusion (EVLP) with the Organ Care System Lung device for evaluation of DCD lungs.

Methods. We performed a retrospective review of the DCD lung transplantation (LTx) experience at a single institution through the use of a prospective database.

Results. From 2011 to 2015, 208 LTx were performed at the University of Alberta, of which 11 were DCD LTx with 7 (64%) that underwent portable EVLP. DCD lungs preserved with portable EVLP had a significantly shorter cold ischemic time (161 ± 44 vs 234 ± 60 minutes, P = .045), lower grade of primary graft dysfunction at 72 hours after LTx (0.4 ± 0.5 vs 2.1 ± 0.7, P = .003), similar mechanical ventilation time (55 ± 44 vs 103 ± 97 hours, P = .281), and hospital length of stay (29 ± 11 vs 33 ± 10 days, P = .610). All patients were alive at 1-year follow-up after LTx with improved functional outcomes and acceptable quality of life compared with before LTx, although there were no intergroup differences.

Conclusions. In our pilot cohort, portable EVLP was a feasible modality to increase confidence in the use of DCD lungs with validated objective evidence of lung function during EVLP that translates to acceptable clinical outcomes and quality of life after LTx. Further studies are needed to validate these initial findings in a larger cohort.

DONATION of organs after circulatory death (DCD) has the potential to significantly alleviate the shortage of transplantable lungs and equate to an extra 28% of donors [1]. Multiple national and international studies have demonstrated comparable survival of DCD lung recipients compared with donation after brain death (DBD) lung recipients [2–6]. Despite this, an analysis of the Scientific Registry of Transplant Recipients from 2006 to 2014 for lung transplantation reports that of 7690 DCD and 58,283 DBD donor lungs, only 162 DCD lungs were used (2.1% of those donated), compared with 12,495 DBD lungs (21.4%) [7].

Non-portable normothermic ex vivo lung perfusion (EVLP) has been used as a technique to prevent lung injury compared with extended cold static preservation [8], assess and recondition suboptimal donor lungs, including DCD lungs, with successful clinical lung transplantation (LTx) [9,10]. The Organ Care System (OCS Lung) (Transmedics) is the only portable device for EVLP that is designed to minimize...
cold ischemic injury [11,12]. Interim results from the OCS Lung INSPIRE trial report significantly decreased primary graft dysfunction (PGD) and in-hospital mortality in DBD donor lungs subject to EVLP when compared with cold static preservation [13].

Barriers for the underutilization of DCD lungs are multifactorial. Barriers have been reported to stem from concerns regarding donor lung quality, logistical and financial challenges of DCD procurement, and the heightened possibility of an aborted procurement caused by prolonged ischemic time and lack of DCD experience by lung transplant programs [7]. Portable EVLP provides the opportunity for remote evaluation and preconditioning of donor lungs, reduced ischemic times, and validated objective evidence of lung function before transplantation. Thus, this technology may play an important role in increasing the willingness of centers to adopt transplantation of DCD organs.

We report herein our pilot experience using portable EVLP for DCD LTx with acceptable recipient functional outcomes and quality life.

METHODS

Study Design

Between December 2011 and November 2015, 208 LTx were performed at the University of Alberta, of which 11 were DCD LTx (Fig 1). DCD donors now account for approximately 8% of our donors in 2015, in which all DCD donors offered to our institution were utilized. The University of Alberta Health Research Ethics Board approved this study. All patients gave consent for the possibility of receiving DCD lungs as well as the potential for ex vivo assessment of lungs at the time of informed consent for their LTx procedure. Our DCD LTx program began with the use of cold static preservation for lung preservation, which was transitioned to the use of EVLP with the availability of the technology during the OCS Lung INSPIRE trial. Since then, we have determined that all DCD lungs should be evaluated through the use of EVLP because they are deemed marginal as per our institution’s consensus. All DCD lungs were of Maastricht category III, controlled withdrawal of life support, or awaiting cardiac arrest [14]. The OCS Lung device is an experimental platform in Canada and was allowed for restricted use by our hospital with informed consent of the patient.

Donor Selection

Donor lung suitability was determined by the same criteria as brain-dead donors. DCD was determined as per national guidelines with institutional approval [15].

Portable EVLP

DCD lungs since 2013 were perfused with portable EVLP, as previously described [11,16], with 100% conversion rate to transplantation. Acceptance of EVLP-evaluated lungs for transplantation was based on criteria as defined by prior studies [9,11,16-18], which include: (1) lung oxygenation capacity with a final ratio of arterial oxygen partial pressure to fractional inspired oxygen (P/F ratio) of 350 mm Hg or greater; (2) deterioration of less than 15% from baseline levels of hemodynamic and respiratory variables (pulmonary vascular resistance, peak airway pressures, and lung compliance); and (3) absence of clinical signs of lung injury (ie, worsening edema, copious purulent secretion suggestive of infection, or bronchial erythema suggestive of aspiration).

Quality-of-Life Outcomes

All patients participated in a prospective cohort study of health-related quality of life (HRQL) [19]. For patients with multiple HRQL assessments, we used the pre-transplant HRQL assessment closest to the transplant date and the post-transplant HRQL assessment done at 3 and 12 months after transplant.

The questionnaire included the Beck’s Depression Inventory (BDI) [20], the Chronic Respiratory Questionnaire (CRQ) [21], and a generic health index, Medical Outcomes Study 36-Item Short Form Health Survey (SF36) [22]. The BDI is a self-administered, 21-item self-report scale that measures manifestations of depression. Scores range from 5 to 63, with lower scores signifying a lower level of depression. The CRQ is an interviewer-administered questionnaire to measure quality of life in patients with chronic respiratory disease. The CRQ consists of a total of 20 items in four different domains including dyspnea, fatigue, emotional function, and mastery, in which a higher score indicates freedom from symptoms. The SF36 yields an 8-scale profile of physical and mental health summary measures, in which a higher score signifies better quality of life.

Statistics

Statistical analyses were performed with the use of SPSS 21 software (IBM Corp). Parametric continuous variables are expressed as mean ± standard deviation and were compared by use of the Student t test. Nonparametric continuous variables are expressed as medians (interquartile range) and were compared by use of the Mann-Whitney test. Categorical variables were compared by use of the χ^2 test.

A 2-sided P value <.05 was considered statistically significant.

RESULTS

From December 2011 to November 2015, 208 LTx were performed at the University of Alberta, of which 11 were DCD LTx. Of these 11 DCD LTx that comprise our study cohort, 7 (64%) recipients received DCD lungs that were subject to EVLP with the portable EVLP device and the remaining 4 patients received lungs that were preserved on ice with the use of standard cold static preservation. DCD donor demographics are described in Table 1. The P/F ratio

![Fig 1. Lung transplantations performed at the University of Alberta (2011–2015), where DCD lungs accounted for approximately 8% of lung donors in 2015.](image-url)
of DCD donors before withdrawal of life support therapy was not significantly different between the EVLP group (367 ± 119) and the no-EVLP group (392 ± 58) (P = .706) (Table 1).

Recipient characteristics are described in Table 2. There were no significant differences in age, sex, body mass index, and diagnosis. One patient in the no-EVLP group was bridged to transplant with extracorporeal membrane oxygenation (ECMO), whereas 3 patients in the EVLP group were bridged to transplant by means of mechanical ventilation.

Donor warm ischemic time was not significantly different between the EVLP group and the no-EVLP group (26 ± 8 vs 27 ± 5 minutes, P = .897) (Fig 2). The portability of the EVLP device allowed a significantly shorter cold ischemic time (161 ± 44 vs 234 ± 60 minutes, P = .045) and a longer preservation time (758 ± 131 vs 518 ± 112 minutes, P = .014) for the EVLP group (Fig 2). There were no significant differences in withdrawal of life support time points and the use of mechanical circulatory support between the two groups (Table 3).

The mean EVLP time was 210 ± 101 minutes. DCD lungs improved in function during the perfusion period. Comparison of initial to final physiologic parameters (Fig 3) demonstrates a decline in pulmonary artery pressure (6 ± 2 to 5 ± 1 mm Hg, P = .193), pulmonary vascular resistance (413 ± 107 to 310 ± 116 dyne-s/cm², P = .111) with a significant improvement in peak airway pressure (16 ± 4 to 11 ± 3 mm Hg, P = .018), dynamic compliance (42 ± 11 to 71 ± 16 mL/cm Hg, P = .002), and P/F ratio (386 ± 107 to 500 ± 83, P = .039). Physiologic parameters such as pulmonary artery pressure and pulmonary vascular resistance are lower than in vivo as a result of the flow rate on the device being approximately 40% of maximal cardiac output.

Early postoperative outcomes (Table 3) were similar in terms of mechanical ventilation time (55 ± 44 vs 103 ± 97 hours, P = .281), intensive care unit stay (6 ± 3 vs 8 ± 4
days, \( P = .427 \)), and hospital length of stay (29 ± 11 vs 33 ± 10 days, \( P = .610 \)) for the EVLP and no-EVLP groups, respectively. However, the P/F ratio at 72 hours after transplantation for the recipients of DCD lungs after EVLP was significantly higher (297 ± 72 vs 160 ± 50, \( P = .009 \)) and the grade of PGD at 72 hours was signifi-
cantly lower (0.4 ± 0.5 vs 2.1 ± 0.7, \( P < .001 \)) (Fig 4).

All patients were alive at 1-year follow-up after DCD lung transplantation. In comparing the EVLP to the no-EVLP group, functional outcomes at 6 months after LTx (Table 4) were acceptable, with ratio of forced expiratory volume in 1 second over forced vital capacity (FEV1/FVC) (98 ± 7 vs 98 ± 6, \( P = .972 \)), 6-minute walk test distance (583 ± 85 vs 373 ± 134 meters, \( P = .051 \)), and a significantly lower Borg Dyspnea Score in the EVLP group (1 ± 1 vs 3 ± 1, \( P = .007 \)). Functional outcomes after LTx with DCD lungs for both groups were comparable to normal reference values [23] for 6-minute walk test distance 572 ± 90 meters and Borg Dyspnea Score 0.5 (range, 0–3). Post-LTx lung function, 6-minute walk test distance, and Borg Dyspnea Score at the individual level at 3 and 6 months were all similar to pre-LTx values, except for the Borg Dyspnea Score, which had a more significant decrease with EVLP (–6 ± 2 vs 0 ± 1, \( P = .006 \)).

Baseline quality of life for recipients of DCD lungs before LTx as measured by the SF36 Physical Component Summary Score was significantly lower than the normal Canadian reference values [22] (28 ± 7 vs 51 ± 9, \( P < .001 \)), demonstrating their physical limitation caused by end-stage lung disease, although they had comparable SF36 Mental Component Summary Scores (49 ± 17 vs 52 ± 9, \( P = .803 \)). HRQL was available for 9 patients (3 no-EVLP, 6 EVLP) at 3 months and 7 patients (2 no-EVLP, 5 EVLP) at 12 months. Both EVLP and no-EVLP DCD lung recipients showed a significant improvement in quality of life after transplantation compared with their pre-transplant levels as measured by the SF36 Physical Component Summary Score.

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**Table 3. Intraoperative Data and Early Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>No EVLP (n = 4)</th>
<th>EVLP (n = 7)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin administered (yes)</td>
<td>2 (50%)</td>
<td>7 (100%)</td>
<td>.040*</td>
</tr>
<tr>
<td>Withdrawal of life support therapy time (min) to:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure &lt;55 mm Hg</td>
<td>17 ± 15</td>
<td>8 ± 5</td>
<td>.156</td>
</tr>
<tr>
<td>Oxygen saturation &lt;70%</td>
<td>3 ± 1</td>
<td>3 ± 2</td>
<td>.902</td>
</tr>
<tr>
<td>Asystole start</td>
<td>26 ± 17</td>
<td>17 ± 5</td>
<td>.212</td>
</tr>
<tr>
<td>Asystole end</td>
<td>31 ± 17</td>
<td>22 ± 5</td>
<td>.218</td>
</tr>
<tr>
<td>EVLP time (min)</td>
<td>–</td>
<td>210 ± 101</td>
<td>–</td>
</tr>
<tr>
<td>MCS support (preoperatively; yes)</td>
<td>1 (25%)</td>
<td>0 (0%)</td>
<td>.200</td>
</tr>
<tr>
<td>MCS support (intraoperatively; yes)</td>
<td>4 (100%)</td>
<td>4 (57%)</td>
<td>.152</td>
</tr>
<tr>
<td>MCS support (postoperatively; yes)</td>
<td>1 (25%)</td>
<td>0 (0%)</td>
<td>.200</td>
</tr>
<tr>
<td>Time on mechanical ventilation (hours)</td>
<td>103 ± 97</td>
<td>55 ± 44</td>
<td>.281</td>
</tr>
<tr>
<td>Required reintubation (yes)</td>
<td>0 (0%)</td>
<td>1 (14%)</td>
<td>.479</td>
</tr>
<tr>
<td>Intensive care unit length of stay (days)</td>
<td>8 ± 4</td>
<td>6 ± 3</td>
<td>.427</td>
</tr>
<tr>
<td>Hospital length of stay (days)</td>
<td>33 ± 10</td>
<td>29 ± 11</td>
<td>.610</td>
</tr>
</tbody>
</table>

*Indicates significance, \( P < .05 \).
Donation after circulatory death LTx without EVLP has been reported to have equivalent early, mid-term, and long-term results as DBD donors, though DCD LTx is still seldom performed [2–6,24]. Despite the shortage of suitable donor organs to meet the demand for lung transplantation, the odds of lungs from DCD donors being used for transplantation are one-tenth the odds of DBD lungs after adjustment for donor organ quality [7]. Given the poor rate of DCD donor utilization, once portable EVLP became available at our center, we examined its utility in increasing the number of DCD lung transplantations performed. In our pilot cohort of patients, we demonstrate that functional re-evaluation of DCD lungs with the use of portable EVLP allows us to confirm good lung function [25] and allows DCD LTx to be done safely with acceptable midterm outcomes and quality of life.

Barriers contributing to the underutilization of DCD lungs include uncertainty regarding donor lung quality, performance in vivo, as well as logistical and financial challenges. Aborted DCD procurement rates have been reported to be as high as 40%, secondary to prolonged ischemic time or failure to progress to death [4]. These aborted lung procurements can cost an average of $18,116.73 per donor without accounting for time of the procurement team and surgeon [7]. EVLP has been used to

![Fig 3.](image-url)
evolve DCD lungs but comes with increased cost to the LTx procedure that must be justified.

Portable EVLP for concomitant preservation, assessment, transport, and repair of DCD lungs may be of potential value in settings of prolonged ischemic time during the DCD procurement process, which remains the main cause for aborted DCD procurements [4]. The unique and detrimental effects of warm ischemia that occur in DCD donors may be mitigated by shortened cold ischemic times through the use of portable EVLP. In addition to being a tool to evaluate potential donor lungs, the normothermic and metabolically active environment restored by portable EVLP provides an ideal platform for therapeutic manipulation [26] and personalized therapy delivery to the DCD organ before transplantation [27].

Although acceptable results can be achieved with conventional preservation of DCD lungs, EVLP can improve the selection process with objective evaluation of lung function to ensure transplant suitability before making a clinical decision to proceed with transplantation. Because EVLP is based on protective ventilation and perfusion, donor lungs that deteriorate on EVLP likely suggest poor donor lung quality, allowing for clinicians to objectively decline the lungs based on function. Yeung et al [28] have preclinical experimental evidence to suggest that transplanting donor lungs that deteriorate on EVLP would lead to severe graft dysfunction after transplantation. Thus, it is conceivable to suggest that the use of portable EVLP to evaluate donor lungs may improve confidence and procurement success as well as prevent adverse events to justify the cost of its use.

Machuca et al [29] demonstrated that non-portable EVLP for DCD lungs was associated with decreased hospital length of stay. We demonstrated similar positive trends with suggestions of a decreased PGD with portable EVLP with the use of DCD lungs, although our ability to decipher this is limited by our small sample size. Despite this, our findings are encouraging, given that the incidence of PGD has been reported to be as high as 25% and remains the main cause of death in the first 30 days after LTx [30]. Given the short donor warm ischemic times and high P/F ratios of the donors in the present study, it is unlikely that portable EVLP had major benefit on the basis of ischemic time alone. The trend toward decreased rates of PGD with the use of EVLP is not elucidated, although, on the basis of current literature, other beneficial processes that occur during EVLP [31–33] may allow for this improvement. As PGD is a significant negative prognostic factor for LTx [30,33] and predictor of bronchiolitis obliterans, which is a major obstacle to long-term survival after LTx [35], longitudinal studies to examine the effect of EVLP on LTx outcomes are eagerly awaited.

A major limitation of our study is that it was a single institutional retrospective study comprising of a small number of patients, as is evident in other DCD series [5,36] and thus is underpowered to draw definitive conclusions. As well, the true significance of our findings is still unclear and may be due to a type 2 error, although at best, we show in a series of recipients that use of EVLP for DCD LTx did not have deleterious effects as confirmed by existing reports [29]. Further studies are required to validate these initial findings in a larger clinical trial such as the proposed International EXPAND Lung Pivotal Trial (EXPANDLung) to examine this in detail.

We conclude that in this pilot cohort, portable EVLP is a feasible method to evaluate DCD lungs with adequate objective evidence of lung function that translates to acceptable in-hospital and 6-month clinical outcomes as well as quality of life after LTx.

### Table 4. Functional and Survival Outcomes

<table>
<thead>
<tr>
<th></th>
<th>No EVLP (n = 4)</th>
<th>EVLP (n = 7)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Months after LTx vs LTx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1%</td>
<td>43 ± 10</td>
<td>36 ± 17</td>
<td>.538</td>
</tr>
<tr>
<td>FVC%</td>
<td>44 ± 20</td>
<td>18 ± 12</td>
<td>.031</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>−29 ± 83</td>
<td>31 ± 44</td>
<td>.164</td>
</tr>
<tr>
<td>6MWT distance</td>
<td>207 ± 152</td>
<td>197 ± 82</td>
<td>.934</td>
</tr>
<tr>
<td>Borg Dyspnea Score</td>
<td>0 ± 1</td>
<td>−5 ± 3</td>
<td>.012</td>
</tr>
<tr>
<td>6 Months after LTx vs LTx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1%</td>
<td>42 ± 4</td>
<td>49 ± 19</td>
<td>.545</td>
</tr>
<tr>
<td>FVC%</td>
<td>50 ± 16</td>
<td>28 ± 16</td>
<td>.086</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>−38 ± 87</td>
<td>37 ± 41</td>
<td>.112</td>
</tr>
<tr>
<td>6MWT distance</td>
<td>194 ± 192</td>
<td>205 ± 115</td>
<td>.927</td>
</tr>
<tr>
<td>Borg Dyspnea Score</td>
<td>0 ± 1</td>
<td>−6 ± 2</td>
<td>.006</td>
</tr>
</tbody>
</table>

Survival at 6 months after LTx

|                         | 4 (100%)       | 7 (100%)    |         |

*Indicates significance, P < .05.
ACKNOWLEDGMENTS

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REFERENCES


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