Ex Vivo Lung Perfusion Allows Successful Transplantation of Donor Lungs From Hanging Victims

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Background. Donor lungs acquired from victims of asphyxiation by hanging are not routinely used for lung transplantation because of the associated lung injury. Ex vivo lung perfusion (EVLP) is a technique to evaluate marginal donor lungs before transplantation. We report here our experience with the use of EVLP in donor lungs procured from victims of asphyxia by hanging.

Methods. Lungs from 5 donors who became brain dead secondary to hanging were evaluated by EVLP. Donor organs were perfused according to trial protocol. Donor lungs were accepted for transplantation if they maintained a PaO₂ greater than or equal to 350 mm Hg, had a clear roentgenogram, and had no significant worsening of physiologic metrics.

Results. Perfused organs included single and double lung blocs, and all were perfused without technical incident. Three of the 5 donor organs evaluated met criteria for transplantation after 3 hours of EVLP and were transplanted. Donor organs rejected for transplantation showed either signs of worsening PaO₂ or deterioration of physiologic metrics. There were no intraoperative complications in the patients who underwent transplantation, and all were alive at 30 days.

Conclusions. We report here the successful use of EVLP to assess donor lungs acquired from victims of asphyxiation by hanging. The use of EVLP in this particular group of donors has the potential to expand the available donor pool. We demonstrate that EVLP is a viable option for evaluating the function of lung allografts before transplantation and would recommend that all donor lungs obtained from hanging victims undergo EVLP to assess their suitability for transplantation.

such as those obtained from hanging victims. We report here our experience with the use of EVLP in evaluating and transplanting lungs obtained from victims of hanging.

Patients and Methods

Donor Organs
Donor lungs in the Normothermic Ex Vivo Lung Perfusion As an Assessment of Extended/Marginal Donor Lungs (NOVEL) trial are deemed marginal by the following criteria: a ratio of PaO$_2$ relative to the fraction of inspired oxygen (FiO$_2$) less than 300 mm Hg at procurement evaluation or 1 or more of the following risk factors: greater than 10 units of blood transfused, radiographic evidence of pulmonary edema, donation after cardiac death, or determined unsuitable for conventional donation by the investigator. All donor organs were offered to all available centers before being considered for the NOVEL lung trial and EVLP.

The donor lungs used for this study were all considered marginal based on the mechanism of brain death of asphyxiation by hanging. Donor lungs were procured in standard fashion using antegrade and retrograde Perfadex flush (XVIVO Perfusion AB, Göteborg, Sweden) [11]. For this study, a total of 5 sets of donor lungs (3 bilateral, 2 single) from victims of hanging were evaluated by EVLP for potential transplantation as part of the ongoing NOVEL trial.

Perfusion Technique
On arrival, a cannula was sewn to the left atrial cuff with 4-0 Prolene suture (Ethicon, Somerville, NJ). Another cannula was inserted in the pulmonary artery and secured with 2-0 silk. An endotracheal tube was inserted in the airway and held in place with umbilical tape. The cannulas and endotracheal tube were then connected to the XVIVO perfusion system, which functions as a combined ventilator and cardiopulmonary bypass machine with the capacity to measure donor lung functional metrics. Air was then removed from the lungs, and perfusion was initiated with Steen solution (XVIVO, Göteborg, Sweden) supplemented with heparin, methylprednisolone, and an antibiotic tailored to the donor's Gram stain results.

Once the lungs reached a temperature of 35℃, ventilation was initiated with tidal volumes of either 7 mL/kg or 3.5 mL/kg for double and single lungs, respectively, based on the donor's ideal body weight. Bronchoscopy was performed at the initiation of lung perfusion and before transplantation. The lungs were evaluated hourly by PaO$_2$/FiO$_2$ and roentgenography. Functional metrics including compliance, pulmonary vascular resistance, and peak airway pressure were evaluated continuously. Following the NOVEL trial protocol, this was continued over a course of 3 to 4 hours.

Inclusion/Exclusion Criteria for Transplantation
Donor lungs accepted for transplantation met the following criteria: PaO$_2$/FiO$_2$ greater than 350 mm Hg and improving for 2 consecutive hours without a 10% decline in the functional metrics of lung compliance, pulmonary vascular resistance, and peak airway pressure.

Results
Donor lungs from 5 individuals whose cause of death was asphyxia secondary to suicidal hanging underwent EVLP evaluation at our institution. All 5 donors met inclusion for entrance into the NOVEL trial because of the mechanism of injury. Additionally, 3 of the donor lungs exhibited PaO$_2$/FiO$_2$ less than 300 mm Hg, with 1 from each of the transplanted and nontransplanted cohorts having PaO$_2$/FiO$_2$ greater than 400 mm Hg. Four of the lung allografts were procured from brain-dead, heart-beating donors. One lung allograft from the nontransplanted cohort was procured after cardiac death.

All 5 donors were found pulseless in the field, requiring cardiopulmonary resuscitation. Total estimated downtime of donors for each of the 3 transplanted lung allografts was 45, 47, and 31 minutes. For the 2 lung allografts that failed to meet transplant criteria, the total estimated downtime of donors was comparable at 45 and 40 minutes, respectively. The characteristics of the donor lungs are found in Table 1.

The decision to transplant the donor lungs after EVLP was based on the NOVEL trial criteria. Three of the donor lungs were transplanted after demonstrating PaO$_2$/FiO$_2$ greater than 350 mm Hg for greater than 2 consecutive hours, acceptable roentgenologic findings, and no deterioration in compliance, pulmonary vascular resistance, or peak airway pressure as demonstrated in the left column of Fig 1.
Two of the donor lungs did not meet these criteria and were therefore not transplanted. One donor allograft demonstrated deterioration of pulmonary vascular resistance and failed to achieve an acceptable PaO2/FiO2. The second donor allograft that did not meet transplant criteria showed an initial improvement in PaO2/FiO2 that subsequently deteriorated. This second donor also demonstrated a worsening peak airway pressure and a posterior segment opacity that failed to resolve on chest roentgenology (Fig 2). The PaO2/FiO2 and physiologic data recorded during EVLP are depicted for both the transplanted and nontransplanted cohorts in Fig 1.

Recipient A
A 63-year-old man with emphysema and an LAS of 30.95 underwent single left lung transplantation. His immediate postoperative PGD score on arrival to the ICU was 2. The patient was extubated 10 hours after his procedure and remained in the ICU for 4 days. He was discharged on postoperative day 9 with no adverse events.

Recipient B
A 53-year-old man with pulmonary fibrosis and an LAS of 85.1 underwent bilateral lung transplantation. His PGD scores were 1 at ICU admission and 1 at 24 hours. He was extubated 35 hours after transplantation and stayed in the ICU for 9 days. He was discharged from the hospital on postoperative day 13 but required readmission for drainage of a right-sided pleural effusion on postoperative day 29.

Recipient C
A 56-year-old woman with emphysema and an LAS of 36.9 underwent bilateral lung transplantation. Her PGD scores were 0 on ICU admission and 1 at 24 hours. This patient required reoperation 7 hours after transplantation for bleeding from the right side of the chest. She was extubated 46 hours after initial transplantation and had no further complications. She remained in the ICU for 3 days and was discharged on postoperative day 7.

Images of a transplanted donor lung and associated roentgenogram while undergoing EVLP are shown in Fig 3. The characteristics of the recipients and postoperative PGD scores are presented in Tables 2 and 3, respectively.

Comment
Lungs from donors who experience brain death secondary to asphyxia by hanging are typically declined for transplantation in the United States. Currently, only 3% to 5% of all lung transplantations in the United States are from donors who died of asphyxiation[2]. It is thought that death from hanging produces significant lung injury, resulting in pulmonary edema from inspiratory efforts against a mechanically obstructed glottis, ultimately causing a decrease in intrathoracic pressure. This entity is referred to in the literature as negative-pressure pulmonary edema or postobstructive pulmonary edema. It can be seen with other mechanisms such as strangulation, foreign body aspiration, and difficult intubation[12].

The pathophysiology responsible for the edema is likely multifold. Based on Starling’s law, the oncotic pressure and hydrostatic pressure of the capillary bed must balance the oncotic and hydrostatic pressure of the interstitium to prevent a net egress of fluid. Attempted inspiration against an obstructed upper airway causes a drop in the intrathoracic pressure, resulting in increased venous return and increased pulmonary capillary pressure, with a concomitant decrease in pulmonary interstitial pressure[7, 13], resulting in pulmonary edema. In a sheep model, Loyd and colleagues[14] showed that lung interstitial fluid increased under conditions of an obstructed airway. The postulated mechanism was increased capillary hydrostatic pressure. Furthermore, Smith-Erichsen and Bo[13] demonstrated that decreasing intrathoracic pressure with an obstructed airway resulted in an increase in alveolar interstitial fluid accumulation. In addition to increased venous return, left ventricular compliance decreases and afterload increases because of the decrease in negative pressure[15]. The resultant increased overall pulmonary blood volume raises the pulmonary capillary hydrostatic

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Table 1. Demographics of Donors With Lungs That Were Transplanted and Not Transplanted

<table>
<thead>
<tr>
<th>Variable</th>
<th>Transplanted</th>
<th>Not Transplanted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>38</td>
<td>20</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Smoking history (pack-years)</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Reason for inclusion for EVLP</td>
<td>Hanging, low PaO2/FiO2</td>
<td>Hanging</td>
</tr>
<tr>
<td>Total estimated downtime after hanging (min)</td>
<td>45</td>
<td>47</td>
</tr>
<tr>
<td>PaO2/FiO2 at procurement (mm Hg)</td>
<td>278</td>
<td>500</td>
</tr>
<tr>
<td>Donor type</td>
<td>Single left</td>
<td>Bilateral</td>
</tr>
</tbody>
</table>

DCD = donation after cardiac death; EVLP = ex vivo lung perfusion.
pressure, further exacerbating the pulmonary edema. Hypoxia associated with hanging increases pulmonary capillary vascular resistance, increasing the hydrostatic pressure [16]. All these factors contribute to the rise in pulmonary capillary hydrostatic pressure, resulting in pulmonary edema.

Although probably less contributory to pulmonary edema in hanging patients, there is evidence to suggest that adrenergic and cytokine response plays a role in the formation of pulmonary edema in hanging victims. Hypoxia induces a hyperadrenergic state, increasing the pulmonary vascular resistance and potentially causing capillary leak [17]. Elevated inflammatory cytokines have also been associated with strangulation [18, 19], which could contribute to loss of capillary integrity.

The incidence of hanging deaths has increased by 52% over the past 10 years, and in 2010 there were more than 9,000 deaths attributed to hanging [20]. Lungs from victims of hanging death are infrequently used for lung transplantation because of the ensuing pulmonary edema and the unpredictable function in the recipient. However, little knowledge exists regarding the true utility of these organs. Other than the theoretical physiologic processes pointing to poor function, the avoidance of these organs is somewhat based on isolated reports of poor outcomes after transplantation [21].

Fig 1. Functional metrics of lungs undergoing ex vivo perfusion. Transplanted lungs (left column) showed improvement in (A) $\text{PaO}_2$/FiO$_2$, (B) static compliance, (C) pulmonary vascular resistance, and (D) peak airway pressure. Lungs with worsening functional metrics were not transplanted (right column). Lines A, B and C represent donor lung allografts transplanted in patients A, B and C respectively. Line D and E represent lung allografts that failed to meet transplant criteria.
EVLP represents an ideal mechanism to test the function of lungs from hanging victims before transplantation because it provides an external low-risk means of observing lung function before transplantation. Many others have demonstrated the efficacy of EVLP in predicting and potentially improving lung function from marginal donors [10, 22–24]. As seen in this cohort of lung alloplants as well as early reports from the NOVEL trial [10], not all lungs assessed by EVLP will be suitable for transplantation. EVLP must be used appropriately with careful assessment of the lung allograft’s gross appearance, roentgenographic findings, and physiologic changes during perfusion before transplantation to ensure the most favorable clinical outcomes. Also, it should be noted that all donor allografts in this study underwent EVLP according to the NOVEL trial protocol [8], which uses Steen solution without red blood cells as the perfusate, and lungs were perfused in a low-flow state approximately 40% of in vivo conditions. Other groups have also demonstrated acceptable outcomes through augmenting the EVLP conditions to more closely represent in vivo physiologic conditions by perfusing at rates closer to full flow and adding red blood cells to make up 10% to 25% of the perfusate [25, 26].

We demonstrate here that organs from hanging victims can be used successfully for transplantation. It is unclear how these lungs that were successfully transplanted escaped the physiologic injury that has been described.

Table 2. Patient Demographics of the 3 Recipients Who Received Lung Transplants After Undergoing Ex Vivo Perfusion from Donors Who Died of Hanging

<table>
<thead>
<tr>
<th>Characteristics of Recipients</th>
<th>Transplant</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Lung allocation score</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single left</td>
<td>63</td>
<td>Male</td>
<td>30.9</td>
<td>Emphysema</td>
</tr>
<tr>
<td></td>
<td>Bilateral</td>
<td>53</td>
<td>Male</td>
<td>85.1</td>
<td>Pulmonary fibrosis</td>
</tr>
<tr>
<td></td>
<td>Bilateral</td>
<td>56</td>
<td>Female</td>
<td>36.9</td>
<td>Emphysema</td>
</tr>
</tbody>
</table>
but it is clear that not all organs from hanging victims are equally affected by the proposed mechanism. Importantly though, 2 of the 5 sets of lungs evaluated by EVLP did exhibit injury to the point that transplantation was not advisable. Neither of these 2 lung allografts were able to maintain PaO2/FiO2 greater than 350 mm Hg, excluding them from transplantation based on the NOVEL criteria. Also, 1 donor lung demonstrated markedly worse pulmonary vascular resistance. The other showed deterioration of peak airway pressure, and a posterior segment contusion did not resolve. Interestingly, PaO2/FiO2 before procurement and downtime after hanging were similar between the transplanted and nontransplanted lung allograft cohorts, although this sample size was too small to quantify statistical significance.

This should highlight the importance of using EVLP in all these types of donor organs so that implanting dysfunctional lungs can be avoided. Our experience clearly establishes the utility of both EVLP and the use of lungs from hanging victims to further expand the donor pool of lungs. Further widespread acceptance of EVLP as an evaluation technique for marginal donors whose lungs may ultimately be used for lung transplantation.

We would like to thank Tracey MacDermott and the Clinical Trials Office for their efforts in managing the protocol and assistance in data collection.

The NOVEL Trial was supported by XVIVO Perfusion, Inc.

References


Table 3. PGD Calculation Based on PaO2/FiO2 and Roentgenographic Findings of Edema

<table>
<thead>
<tr>
<th>Recipient</th>
<th>ICU Admission</th>
<th>24 Hours After Operation</th>
<th>48 Hours After Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient A</td>
<td>2</td>
<td>Exubated</td>
<td>Exubated</td>
</tr>
<tr>
<td>Patient B</td>
<td>1</td>
<td>1</td>
<td>Exubated</td>
</tr>
<tr>
<td>Patient C</td>
<td>0</td>
<td>0</td>
<td>Exubated</td>
</tr>
</tbody>
</table>

PGD 1 is PaO2/FiO2 greater than 300 mm Hg without edema. PGD 2 is PaO2/FiO2 greater than 300 mm Hg with edema. PGD 3 is PaO2/FiO2 less than 200 mm Hg with edema. PaO2 values are adjusted for the barometric pressure of Denver, Colorado.

ICU = intensive care unit; PGD = primary graft dysfunction.