A successful 24-hour preservation for human lung lobar transplantation leveraging 10-degree cold storage and ex vivo lung perfusion

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Title
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Glossary of Abbreviations

EVLP: Ex vivo lung perfusion
TLC: Total lung capacity
pO2: Partial pressure of oxygen
PV: Pulmonary vein
CIT: Cold ischemia time
PGD: Primary graft dysfunction
Central Picture

10°C preservation and EVLP enable donor lung preservation for over 24 hours.

Central Message

We successfully transplanted donor lungs, evaluated through EVLP and preserved at 10°C for a total preservation time exceeding 24 hours, into the optimal recipient, achieving favorable outcomes.
We report a case of successful cadaveric bilateral lobar lung transplantation (right upper+right middle lobe and left upper lobe) with a total preservation time exceeding 24 hours, facilitated by EVLP (ex vivo lung perfusion) and preservation of donor lungs at 10°C. Informed consent was secured for publication, and Institutional Review Board (IRB) approval was not required as per institutional policies.

Case Presentation:
The donor was a 37-year-old male with brain death due to drug overdose. Additionally, he had a smoking history of 33 pack-years and was declined by multiple centers in the US. His predicted total lung capacity (TLC) was 9.2L. The first recipient chosen for bilateral lung transplantation was a 64-year-old male with chronic obstructive pulmonary disease. The donor lung procurement was performed during daytime, where the cross clamp was applied at 9:30 am. Bilateral lungs were procured by the local retrieval team at the donor hospital and then placed in isolation bags filled with cold Perfadex® solution. They were stored on ice in a cooler box and airlifted to our hospital using this standard preservation. Since we were not familiar with the donor team we decided to assess the lungs on EVLP prior to assessment. Therefore, at 2:52 pm on the same day, EVLP was initiated for donor lungs’ evaluation with our protocol, but bilateral lower lobe edema became pronounced, and oxygenation was found to be poor (Supplemental figure 1) (1). The delta partial pressure of oxygen(pO2) (pO2 post lung − pO2 pre lung) was 320 mmHg after 2 hours of EVLP. However, the differential delta pO2s assessing the oxygenation of each pulmonary veins showed 386 mmHg for the right upper pulmonary vein (PV), 385 mmHg for the right lower PV, and 421 mmHg for the left upper PV. The value for the left lower upper PV was low at 92 mmHg (Supplemental table 1). Given the quality of the lungs, as the bilateral upper and middle lobes exhibited good function, we opted for bilateral lobar lung transplantation (right upper+right middle lobe and left upper lobe) and changed the original recipient to a second recipient, considering the size mismatch. The second recipient was a 65-year-old female with idiopathic pulmonary fibrosis. Her predicted TLC was 5.2L, and the actual TLC was 2.0L. From 8:00 pm after the conclusion of EVLP, the donor lungs were placed in cold storage at 10°C (OR refrigerator set at 10°C, central picture). During that time, the recipient underwent preoperative examinations, and the operation commenced at 6:13 am on following day. Central veno-arterial extracorporeal membrane oxygenation was established after clamshell thoracotomy. Right lobar transplantation began at 7:58 am, and right lung reperfusion resumed at 8:55 am. The total preservation time for the right lobes was 23 hours and 25 minutes. At 9:55 am, left lung lobar transplantation started, and left lung reperfusion resumed at 10:51 am, resulting in a total preservation time of 25 hours and 21 minutes. Extracorporeal circulation time was 3
5 hours and 55 minutes, operation time was 5 hours and 45 minutes, and estimated blood loss was 500 ml. The timeline of this case is shown in Figure 1. The postoperative course was favorable; the patient was extubated on the 4th hospital day and discharged home on the 21st hospital day. After 24-, 48-, and 72-hours post-transplantation, the PGD scores were all 1. Representative chest x-rays are shown in Figure 2.

Conclusion

With the increasing number of lung transplants, it is anticipated that ischemic time can be prolonged due to the organ transport and the transplantation logistics. We have reported that this preservation method that combines optimal cold storage at 10 °C and EVLP may contribute to significant extension of preservation times facilitating an upsurge in lung transplants and enhance postoperative results in the future. This concept was first described by our group in a large animal model of 3 days preservation (2). The results of a clinical trial (NCT04616365), which involved collaboration between Toronto General Hospital and the centers in Madrid and Vienna, have demonstrated promising outcomes with lung preservation at 10°C (3). This preservation method is thought to be superior to conventional methods in preventing mitochondrial dysfunction (4). Furthermore, the 10°C preservation affords us an extended timeframe after donor lung removal. While recipients are typically chosen before donor surgery, the 10°C preservation might allow the selection of the most suitable recipient after a thorough protocolized comprehensive evaluation of donor lungs by EVLP. This, in turn, integrates time allowance for selecting the optimal recipient into the process, facilitating efficient utilization of donor lungs. This may be challenging with the current allocation system, but if long-term preservation of donor lungs becomes common, it might become possible. A larger flexibility of ischemic times after EVLP (2nd CIT) using 10°C can also enable the initiation of lung transplantation during the daytime or transport organs from organ repair centers to transplant centers at longer distances. Based on this case report, we demonstrate that this organ preservation method has the potential to significantly contribute to the improvement of transplant logistics and outcomes.


Figure legends

Figure 1
The timeline from donor surgery to the completion of lung transplantation surgery. The donor lungs were preserved on ice until the initiation of EVLP from the cross-clamp. During EVLP, the lungs were perfused with Steen solution at 37°C.

Figure 2
Perioperative radiograph of the second recipient. A, Preoperative radiograph taken before lung transplant surgery; B, Postoperative radiograph taken on postoperative day 2; C, Postoperative radiograph taken on postoperative day 28. Postoperative radiographs shows good-size matching and aeration of both lung grafts.

Supplemental figure 1
X-ray images of the donor lungs after 1 and 2 hours following the initiation of EVLP. Edema in the bilateral lower lobes of the donor lungs was gradually becoming apparent. The areas of reduced radiolucency, indicating edema, were enclosed by dashed lines in the X-ray images.
**Supplemental table 1**

The parameters during EVLP.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1h</th>
<th>2h</th>
<th>3h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time after EVLP initiation (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery pressure (mmHg)</td>
<td>8</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Left atrial pressure (mmHg)</td>
<td>5</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Peak airway pressure (cmH2O)</td>
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<td>15</td>
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<tr>
<td>Mean airway pressure (cmH2O)</td>
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<td>8</td>
</tr>
<tr>
<td>Plateau airway pressure (cmH2O)</td>
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<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Dynamic lung compliance (ml/H2O)</td>
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<td>91</td>
</tr>
<tr>
<td>Static lung compliance (ml/H2O)</td>
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<td>159</td>
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<tr>
<td>Systemic Delta pO2 (mmHg)</td>
<td>310</td>
<td>320</td>
<td>362</td>
</tr>
<tr>
<td>Perfusate Loss (ml)</td>
<td>100+350</td>
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<td>100</td>
</tr>
<tr>
<td>Right SPV</td>
<td>-</td>
<td>386</td>
<td>-</td>
</tr>
<tr>
<td>Right IPV</td>
<td>-</td>
<td>385</td>
<td>-</td>
</tr>
<tr>
<td>Left SPV</td>
<td>-</td>
<td>421</td>
<td>-</td>
</tr>
<tr>
<td>Left IPV</td>
<td>-</td>
<td>92</td>
<td>-</td>
</tr>
</tbody>
</table>

Storage for over 24 hours
Day X-1

- Start Donor Surgery: 7:32 am
- Start EVLP: 2:52 pm
- Hospitalization of the 2nd recipient: 9:30 pm
- Start pre-OP work up

Day X

- Start LTx surgery: 6:00 am
- Start right lobar LTx: 7:58 am
- End of right lobar LTx: 8:55 am
- End of LTx surgery: 11:58 am

- 10°C preservation: 11 hours (660 mins)
- Decision of the 2nd recipient

- Cross-clamp

- 1st lung total preservation time: 23 hours and 25 minutes (1,405 mins)

- 2nd lung total preservation time: 25 hours and 21 minutes (1,521 mins)

LTx: Lung transplantation
Pre-OP work up: pre operative work up