Ex vivo Lung Perfusion
Methods, Options and Indications

Pablo Sanchez, MD PhD
Lung Transplantation in the U.S. and Sources of Donors

LAS

2 % of all Lung Tx.
Compromise
Lung Quality
Brain Death
Hypotension
Trauma
Mechanical Ventilation
Pneumonia
Aspiration
Not Transplantable
Transplantable
Ex Vivo Lung Perfusion to identify viable Lungs

75%
25%
<table>
<thead>
<tr>
<th>Lung Donor Criteria</th>
<th>(n)</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥55</td>
<td>988</td>
<td>9.3%</td>
</tr>
<tr>
<td>PO2≤300</td>
<td>2937</td>
<td>27.5%</td>
</tr>
<tr>
<td>History Cigarette 20 Pack Years</td>
<td>1207</td>
<td>11.3%</td>
</tr>
<tr>
<td>Chest XRay Abnormal</td>
<td>4900</td>
<td>45.9%</td>
</tr>
<tr>
<td>Purulent Secretions on Bronchscopy</td>
<td>1425</td>
<td>13.4%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>687</td>
<td>6.4%</td>
</tr>
<tr>
<td>Culture Confirmed Blood Infection</td>
<td>584</td>
<td>5.5%</td>
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</table>

<table>
<thead>
<tr>
<th>Guideline Variances</th>
<th></th>
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<tbody>
<tr>
<td>0</td>
<td>2,779</td>
<td>26.0%</td>
</tr>
<tr>
<td>1</td>
<td>4,275</td>
<td>40.1%</td>
</tr>
<tr>
<td>2</td>
<td>2,592</td>
<td>24.3%</td>
</tr>
<tr>
<td>3</td>
<td>835</td>
<td>7.8%</td>
</tr>
<tr>
<td>4</td>
<td>172</td>
<td>1.6%</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>0.1%</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>0.0%</td>
</tr>
</tbody>
</table>
Ex vivo lung perfusion in clinical lung transplantation

2001
New Donor Source
Steen
Transplantation of lungs from a non-heart-beating donor

**Donor**: patient dying of acute myocardial infarction in a cardiac intensive-care unit after failed cardiopulmonary resuscitation. (Type II)

**Preservation**: intrapleural cooling was started 65 min after death. After 3 hrs, the body was transported to the operating theatre and the heart-lung block removed.

**The lungs were assessed ex vivo.**

**Recipient**: 54-year-old woman with chronic obstructive pulmonary disease.
Vivoline (Swedish Method)

- 100% Cardiac Output flow to PA
- Roller Pump
- Left Atrium left open
- Steen Solution™ + Blood (Hto 15%)
- Lungs Transported Cold
  - EVLP at Transplanting Center
- Short Term Perfusion
Ex vivo lung perfusion in clinical lung transplantation

Steen
High Risk Donors
2006

2001
New Donor Source
Steen
## Ex vivo evaluation of non-acceptable donor lungs

<table>
<thead>
<tr>
<th>Donor lung</th>
<th>In situ ( \text{FiO}_2 = 1.0 )</th>
<th>Ex vivo ( \text{FiO}_2 = 0.21 )</th>
<th>Ex vivo ( \text{FiO}_2 = 0.5 )</th>
<th>Ex vivo ( \text{FiO}_2 = 1.0 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31</td>
<td>13.6</td>
<td>35</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>17.4</td>
<td>13</td>
<td>34.3</td>
<td>46.6</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
<td>11</td>
<td>33</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>13.5</td>
<td>39</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>29.8</td>
<td>12</td>
<td>21</td>
<td>46</td>
</tr>
<tr>
<td>6</td>
<td>22.7</td>
<td>8.7</td>
<td>14.7</td>
<td>39</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>26.7 ± 2.5</td>
<td>12.0 ± 0.8</td>
<td>29.5 ± 3.9</td>
<td>54.9 ± 5.1</td>
</tr>
<tr>
<td>Median (range)</td>
<td>27.4 (17.4–34)</td>
<td>12.5 (8.7–13.6)</td>
<td>33.7 (14.7–39)</td>
<td>56.3 (39–66)</td>
</tr>
</tbody>
</table>

### EVLP to Evaluate de Unused Donor Pool

- EVLP: Ex Vivo Lung Perfusion
- Thorac: Thoracic
- Surg: Surgery

Ann Thorac Surg. 2006 February
Ex vivo lung perfusion in clinical lung transplantation

- 2001: New Donor Source
  - Steen

- 2006: High Risk Donors
  - Steen

- 2008: Prolonged EVLP
  - Cypel
Technique for prolonged normothermic ex vivo lung perfusion
XVIVO Perfusion (Toronto Method)

- 40% Cardiac Output flow to PA
- Centrifugal Pump
- Left Atrium closed
- Steen Solution™
- Lungs Transported Cold
- EVLP at Transplanting Center
- Extended Perfusion
Ex vivo lung perfusion in clinical lung transplantation

2001
New Donor Source
Steen

2006
Steen
High Risk Donors

2008
Prolonged EVLP
Cypel

2009
Cypel
High Risk Donors
HELP Trial

2009
2011
NOVEL Trial
High Risk Donors
6 U.S. Centers
<table>
<thead>
<tr>
<th>HELP Toronto</th>
<th>NOVEL Multicenter U.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk Donors</td>
<td>High Risk Donors</td>
</tr>
<tr>
<td>Re-Assessed with EVLP</td>
<td>Re-Assessed with EVLP</td>
</tr>
<tr>
<td>87% conversion rate (20/23)</td>
<td>53% conversion rate (40/76)</td>
</tr>
<tr>
<td>Compared to Standard Donors Standard Preservation</td>
<td>Compared to Standard Donors Standard Preservation</td>
</tr>
<tr>
<td>PGD 3 at 72hrs 30 Day Mortality</td>
<td>30 Day Mortality</td>
</tr>
<tr>
<td>Health Canada approval</td>
<td>FDA HDE approval 2014</td>
</tr>
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</table>
STEEN Solution™ with XPS™

Customized software to monitor physiology

In-line gas monitoring

CardioHelp

Touch-screen display

ICU Ventilator

Heater/cooler (15-39°C)
Physiological Parameters Assessed

PvO₂ and PaO₂

delta PaO₂ > 350 mmHg

Airway pressures

Static and dynamic compliance

Pulmonary vascular resistance
### NOVEL trial Primary Endpoint

<table>
<thead>
<tr>
<th></th>
<th>EVLP n=42</th>
<th>Control n=42</th>
<th>ISHLT Reference</th>
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<tbody>
<tr>
<td>30 day patient survival</td>
<td>98%</td>
<td>100%</td>
<td>94%</td>
</tr>
<tr>
<td>90 day patient survival</td>
<td>98%</td>
<td>100%</td>
<td>88%</td>
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</table>
NOVEL trial Secondary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>EVLP n=42</th>
<th>Control n=42</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGD 3* 72 hrs</td>
<td>5%</td>
<td>3%</td>
<td>NS</td>
</tr>
<tr>
<td>Mech. Ventilation, days</td>
<td>1 1-196</td>
<td>1 1-29</td>
<td>NS</td>
</tr>
<tr>
<td>ECMO</td>
<td>5%</td>
<td>2%</td>
<td>NS</td>
</tr>
<tr>
<td>ICU Stay, days</td>
<td>3 1-197</td>
<td>2.5 1-144</td>
<td>NS</td>
</tr>
<tr>
<td>Hospital Stay, days</td>
<td>13 4-198</td>
<td>11 6-236</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Intraoperative ECMO not considered for this analysis
Brain death
45 years old
Female
Down time 25 minutes

PO$_2$ 350 mmHg
Bilateral Chest X-ray infiltrates

Reason for EVLP: Drowning, unknown time in water
Worsening PO$_2$ despite management
(450 to 350 in 24 hrs.)
Double Lung Tx after using EVLP

65 years old
Female
COPD
LAS 36

PGD 0-1 in the first 72 hrs

Follow up 650 days
Ex vivo lung perfusion in clinical lung transplantation

- New Donor Source (2001): Steen
- Prolonged EVLP (2008): Cypel
- HELP Trial (2009): High Risk Donors
- International Standard Donors INSPIRE Trial (2012)
- NOVEL Trial (2011): High Risk Donors
  - 6 U.S Centers
Primary Graft Dysfunction
2.5 L/min flow to PA

Pulsatile Pump

Left Atrium left open

Low Potassium Dextran + Blood (Hto 15%)

Lungs transported during Perfusion

Extended perfusion
Ex vivo lung perfusion in clinical lung transplantation

- New Donor Source
  - Steen
  - High Risk Donors
    - 2006

- Prolonged EVLP
  - Cypel
  - 2008

- High Risk Donors
  - HELP Trial
    - 2009

- Cypel
  - 2006

- High Risk Donors
  - INSPIRE Trial
    - 2012
  - 2011

- NOVEL Trial
  - High Risk Donors
    - 6 U.S Centers
  - 2011

- 2013
  - Expand Trial
    - High Risk Donors
      - International
## INSPIRE Multicenter vs. Expand Multicenter

<table>
<thead>
<tr>
<th></th>
<th>INSPIRE Multicenter</th>
<th>Expand Multicenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard Donors</td>
<td></td>
<td>High Risk Donors</td>
</tr>
<tr>
<td>Transported EVLP</td>
<td></td>
<td>Re-Assessed with EVLP during transport</td>
</tr>
<tr>
<td>Compared to Standard Donors Standard Preservation</td>
<td></td>
<td>Compared to Standard Donors Standard Preservation</td>
</tr>
<tr>
<td>Composite Survival at Day-30</td>
<td>Absence of PGD 3 first 72 hours</td>
<td>Composite Survival at Day-30 Absence of PGD 3 first 72 hours</td>
</tr>
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Ex vivo lung perfusion in clinical lung transplantation

2001
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2009
HELP Trial

2011
NOVEL Trial
High Risk Donors
6 U.S Centers

2012
INSPIRE Trial
Standard Donors

2013
Expand Trial
High Risk Donors
International

2014
International
Multicenter
High Risk Donors
Extended NOVEL
Standing Questions in EVLP:

1- Full Flow, 40% or 2.5 L/min?

2- Open or closed atrium?

3- Acellular or cellular perfusate?

4- Short or Long term EVLP?

5- EVLP at transplant center or EVLP during transport?
Extending the Preservation and Assessment Time of Donor Lungs Using the Toronto EVLP System™ at a Dedicated Ex Vivo Lung Perfusion (EVLP) Facility

High-Risk Donors
Re-assessed with EVLP (Toronto Method)
Lungs Procured and Shipped to Perfusix
Perfusix does EVLP assessment
Lungs Shipped back to Transplant Center
Service provided for a fee
Who Should Pump?

What is the reason we are pumping:

- **Preservation** of lung organ

- **Assess** Lung Organ Function & **Quality**

- **Treat** Lung disease
  - pulmonary edema
  - pneumonitis
  - pneumonia
  - contusions

**Technical Act**
Ex Vivo Lung Perfusion

**Clinical Act**
Ex Vivo Lung Assessment and Treatment

Courtesy of Frank D’Ovidio
Who Should Pump?

- **Technical Act**
  - Ex Vivo Lung **Perfusion**
  - **Technician?**

- **Clinical Act**
  - Ex Vivo Lung **Assessment and Treatment**
  - **Lung-Tx Clinician?**

  - **Liability**
  - **Patient Responsibility**
  - **Clinical Outcomes**

Courtesy of Frank D’Ovidio
Published clinical outcomes show safety for all systems

Regulatory

Logistical

Economical

Center Preference

May determine System or Systems used at different institutions
Thank you!

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