Ex Vivo Lung Perfusion: Increasing Utilization of Marginal Lungs

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DISCLOSURE

• Vitrolife, XVIVO Perfusion – Research support and clinical trial
• Co-founder and Medical Officer Perfusix Canada and United States
• Co-founder XOR Toronto Labs
First Successful Lung Transplantation in the World
Toronto General Hospital 1983
G Pearson, J Cooper, A Patterson, T Todd
First Lung Tx

First Double Lung Tx
Indications (TGH) N=1450

- Eisenmenger's: 3%
- Cystic Fibrosis: 22%
- ILD/IPF: 31%
- Other: 3%
- Re-Tx: 3%
- COPD/Emphysema: 33%
- PAH: 5%
- BAC: 1%
- ILD/IPF: 31%
Major Obstacle for Lung Transplantation Success

- Absence of sufficient organs to meet the growing demand!
- Up to 30% patients die on wait lists
- Larger number of patients are not even listed
3 Years Post LTx
Low Utilization Rates

BDD = 17%

DCD = 2%
Figure 1: Injuries to donor lungs in potential multiorgan donors

Clinical Problem - PGD
Folkert Belzer
Fathers of Hypothermic Preservation
Reduction of cell metabolism by 95%
Manipulate Storage Temperature According to Organ / Clinical Needs: Hypothermic - Normothermic

• Time to accurately assess, diagnose (improve utilization)
• Option to treat, recover, repair (targeted)
• Opportunity to reassess → confirm results of treatment
SPECIAL ARTICLES

THE CULTURE OF WHOLE ORGANS

The method to be described consists of the transplantation of an organ or of any part of the body into a sterile chamber, and of its artificial feeding with a nutrient fluid through the arteries. It is not in any way a substitute for the method of tissue culture. Its techniques, as well as its purposes, are quite different. As is well known, tissues and blood cells grow like bacteria in flasks containing appropriate media. The techniques for the cultivation of tissues are somewhat analogous to bacteriological techniques, although far more delicate. But it is through the employment of complex mechanical and surgical procedures that organs are enabled to live isolated from the body. Tissue culture deals with cells as units of bodily structures; the new method, with cellular societies as organic wholes. Its ultimate purposes are the manufacture in vitro of the secretions of endocrine glands, the isolation of the substances essential to the growth, differentiation and functional activity of those glands, the discovery of the laws of the association of organs, the production in vitro and the treatment of organic and arterial diseases, etc.

The idea of maintaining alive a portion of the body in order to study its functions is not new. In 1812, the physiologist Le Gallois¹ wrote that, “if one could sub-

Lindbergh, Science, 1935
Twelve Hour Perfusion of Isolated Pulmonary Lobes*

Figure 2. Mean pulmonary artery pressures in 12 hour lung perfusion.

Figure 3. Mean pulmonary vascular resistance in 12 hour lung perfusion.

CHEST, VOL. 60, NO. 1, JULY 1971

Couves, CM
Transplantation of lungs from a non-heart-beating donor

Stig Steen, Trygve Sjöberg, Leif Pierre, Qiuming Liao, Leif Eriksson, Lars Algotsson

Lancet 2001; 357: 825–29

Figure 1: Schematic drawing of lung assessment ex vivo
PAP=pulmonary-arterial pressure; LAP=left-arterial pressure.
TORONTO EX VIVO LUNG PERFUSION (EVLP) SYSTEM

Gas for Deoxygenation
86% N₂, 8% CO₂, 6% O₂

Red: Venous (Oxygenated) perfusate
Blue: Arterial (Deoxygenated) perfusate
Perfusate: Acellular Steen Solution

Reservoir
Leukocyte filter
Pump
Bridge
Membrane
(De)oxygnerator
XVIVO Chamber with Lungs
ICU Ventilator

Perfusion: 40% CO, LAP 5mmHg, PAP 10-12mmHg
Ventilation: 7cc/kg, 7BPM, PEEP 5, FiO₂ = 21%

Toronto Sky Dome

Toronto XVIVO™ System
DEVELOPMENT OF A STABLE AND RELIABLE EX VIVO LUNG PERFUSION TECHNIQUE

NORMOTHERMIC EX VIVO PERFUSION INTERRUPTS COLD ISCHEMIC INJURY (24h)

Normothermic Ex vivo Lung Perfusion in Clinical Transplantation – HELP Trial
Normothermic Ex Vivo Lung Perfusion in Clinical Lung Transplantation

Marcelo Cypel, M.D., Jonathan C. Yeung, M.D., Mingyao Liu, M.D., Masaki Anraku, M.D., Fengshi Chen, M.D., Ph.D., Wojtek Karolak, M.D., Masaaki Sato, M.D., Ph.D., Jane Laratta, R.N., Sassan Azad, C.R.A., Mindy Madonik, C.C.P., Chung-Wai Chow, M.D., Cecilia Chaparro, M.D., Michael Hutcheon, M.D., Lianne G. Singer, M.D., Arthur S. Slutsky, M.D., Kazuhiro Yasufuku, M.D., Ph.D., Marc de Perrot, M.D., Andrew F. Pierre, M.D., Thomas K. Waddell, M.D., Ph.D., and Shaf Keshavjee, M.D.
Study Logistics

Donor Lungs Referred for EVLP

Cold Ischemic Time 1 (transportation)

EVLP for 4-6h
P/F>400mmHg, stable or improved PawP, PVR, Compliance, X-ray

Cold Ischemic Time 2

Transplantation
<table>
<thead>
<tr>
<th>Case#</th>
<th>Age (years)</th>
<th>Cause of death</th>
<th>Donor type</th>
<th>Transplant type</th>
<th>Smoking (Pack/year)</th>
<th>Chest X-ray</th>
<th>Bronchoscopy</th>
<th>Microbiology (BAL)</th>
<th>Best PO2/FiO2 (mmHg)</th>
<th>Direct examination of the lungs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>Trauma</td>
<td>BDD</td>
<td>Bilateral</td>
<td>0</td>
<td>Right lower lobe opacity, Diffuse bilateral infiltrates</td>
<td>Bloody secretions</td>
<td>Negative</td>
<td>262</td>
<td>Edema on palpation</td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>CVA</td>
<td>BDD</td>
<td>Bilateral</td>
<td>0</td>
<td>Diffuse perihilar infiltrates</td>
<td>Airway erythema</td>
<td>H Flu</td>
<td>233</td>
<td>Edema on palpation</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>Trauma</td>
<td>DCD</td>
<td>Bilateral</td>
<td>0</td>
<td>Left lung consolidated</td>
<td>Mucoid secretions</td>
<td>H flu</td>
<td>355</td>
<td>Contusion left lung</td>
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<tr>
<td>4</td>
<td>22</td>
<td>Trauma</td>
<td>DCD</td>
<td>Single</td>
<td>0</td>
<td>Diffuse lower lobe infiltrates</td>
<td>Bloody secretions</td>
<td>MSSA; H flu</td>
<td>386</td>
<td>Edematous; contusions left lung</td>
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<tr>
<td>5</td>
<td>48</td>
<td>CVA</td>
<td>BDD</td>
<td>Bilateral</td>
<td>0</td>
<td>Right lower lobe infiltrate</td>
<td>Mucoid secretions</td>
<td>MSSA; H flu</td>
<td>300</td>
<td>Consolidation; edema right lower lobe</td>
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<tr>
<td>6</td>
<td>45</td>
<td>Anoxia/Arrest</td>
<td>DCD</td>
<td>Bilateral</td>
<td>10</td>
<td>Clear</td>
<td>Clear</td>
<td>Negative</td>
<td>492</td>
<td>Normal</td>
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<tr>
<td>7</td>
<td>68</td>
<td>Anoxia/Arrest</td>
<td>DCD</td>
<td>Bilateral</td>
<td>0</td>
<td>Clear</td>
<td>Muco-purulent secretions</td>
<td>Negative</td>
<td>334</td>
<td>Edema; redness in lower lobes</td>
</tr>
<tr>
<td>8</td>
<td>21</td>
<td>CVA</td>
<td>BDD</td>
<td>Single</td>
<td>0</td>
<td>Heavy infiltrates right lung</td>
<td>Mucoid secretions</td>
<td>MSSA</td>
<td>252</td>
<td>Consolidation RLL</td>
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<td>9</td>
<td>17</td>
<td>Trauma</td>
<td>Single</td>
<td>Bilateral contusions</td>
<td>0</td>
<td>Bilateral contusions</td>
<td>Bloody secretions</td>
<td>MSSA</td>
<td>254</td>
<td>Bilateral contusions--;edema</td>
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<tr>
<td>10</td>
<td>40</td>
<td>Anoxia/Arrest</td>
<td>DCD</td>
<td>Bilateral</td>
<td>15</td>
<td>Clear</td>
<td>Massive charcoal aspiration</td>
<td>Negative</td>
<td>479</td>
<td>Charcoal tinged</td>
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<tr>
<td>11</td>
<td>23</td>
<td>Anoxia/Arrest</td>
<td>BDD</td>
<td>Bilateral</td>
<td>0</td>
<td>Atelectasis, Bilateral infiltrates</td>
<td>Mucoid secretions</td>
<td>MSSA</td>
<td>160</td>
<td>Large amount of clots in pulmonary artery</td>
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<tr>
<td>12</td>
<td>27</td>
<td>Trauma</td>
<td>BDD</td>
<td>Single</td>
<td>5</td>
<td>Large consolidation on left lung and small on right lung</td>
<td>Purulent secretions right</td>
<td>MSSA; H flu</td>
<td>282</td>
<td>Left lung massive contusion (only right lung perfused)</td>
</tr>
<tr>
<td>13</td>
<td>38</td>
<td>CVA</td>
<td>BDD</td>
<td>Bilateral</td>
<td>0</td>
<td>Clear CXR; Massive pulmonary emboli on CT chest</td>
<td>Mucoid secretions</td>
<td>Negative</td>
<td>469</td>
<td>Normal</td>
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<tr>
<td>14</td>
<td>49</td>
<td>CVA</td>
<td>BDD</td>
<td>Bilateral</td>
<td>0</td>
<td>Opacity in left lower lobe</td>
<td>Purulent secretions</td>
<td>MSSA</td>
<td>336</td>
<td>Normal</td>
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</table>
Bronchoscopy
Lung Xray
Total Preservation Period

Medians and ranges
Early outcomes were similar in the 2 groups

<table>
<thead>
<tr>
<th>End Point</th>
<th>EVLP Lungs (N = 20)</th>
<th>Control Lungs (N = 116)</th>
<th>Absolute Difference†</th>
<th>P Value‡</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Donors without a Heartbeat (N = 9)</td>
<td>Brain-Dead Donors (N = 11)</td>
<td>Total (N = 20)</td>
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<td><strong>Primary end point§</strong></td>
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<tr>
<td>PGD grade 2 or 3 at 72 hr (%)</td>
<td>11</td>
<td>18</td>
<td>15</td>
<td>30</td>
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<tr>
<td><strong>Secondary end points§</strong></td>
<td></td>
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<td></td>
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<tr>
<td>PGD grade 2 or 3 at ICU arrival (%)</td>
<td>33</td>
<td>18</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>PGD grade 2 or 3 at 24 hr (%)</td>
<td>11</td>
<td>18</td>
<td>15</td>
<td>36</td>
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<tr>
<td>PGD grade 2 or 3 at 48 hr (%)</td>
<td>33</td>
<td>27</td>
<td>30</td>
<td>35</td>
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<tr>
<td>ECMO (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>PaO₂:FiO₂ on arrival in ICU (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>420</td>
<td>423</td>
<td>422</td>
<td>372</td>
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<tr>
<td>Range</td>
<td>85–518</td>
<td>86–538</td>
<td>85–538</td>
<td>49–591</td>
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<tr>
<td>Mechanical ventilation after transplantation (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Range</td>
<td>1–27</td>
<td>1–101</td>
<td>1–101</td>
<td>1–43</td>
</tr>
<tr>
<td>ICU stay after transplantation (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Range</td>
<td>1–34</td>
<td>1–101</td>
<td>1–101</td>
<td>1–103</td>
</tr>
<tr>
<td>Hospital stay after transplantation (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>19</td>
<td>34</td>
<td>23</td>
<td>27</td>
</tr>
<tr>
<td>Range</td>
<td>7–54</td>
<td>11–101</td>
<td>7–101</td>
<td>9–156</td>
</tr>
</tbody>
</table>
Overall survival

Control (n=116)  EVLP (n=23)

p=0.77

median f/u 635 days
### TABLE 2. Recipient outcomes in ex vivo lung perfusion and conventional transplants

<table>
<thead>
<tr>
<th>Variable</th>
<th>EVLP (n = 50)</th>
<th>Controls (n = 253)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>PGD 3 at 72 h (%)</td>
<td>2</td>
<td>8.5</td>
<td>.14</td>
</tr>
<tr>
<td>ECLS (%)</td>
<td>2</td>
<td>2.7</td>
<td>1.00</td>
</tr>
<tr>
<td>Mechanical ventilation (d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2</td>
<td>2.2</td>
<td>.30</td>
</tr>
<tr>
<td>Range</td>
<td>1-101</td>
<td>1-43</td>
<td></td>
</tr>
<tr>
<td>ICU stay (d)</td>
<td></td>
<td></td>
<td>.32</td>
</tr>
<tr>
<td>Median</td>
<td>4</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1-100</td>
<td>1-257</td>
<td></td>
</tr>
<tr>
<td>Hospital stay (d)</td>
<td></td>
<td></td>
<td>.11</td>
</tr>
<tr>
<td>Median</td>
<td>20</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>7-156</td>
<td>1-299</td>
<td></td>
</tr>
<tr>
<td>30-d mortality (%)</td>
<td>4</td>
<td>3.5</td>
<td>1.00</td>
</tr>
<tr>
<td>Anastomotic stricture requiring</td>
<td>4</td>
<td>4</td>
<td>1.00</td>
</tr>
<tr>
<td>intervention (%)</td>
<td></td>
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</tr>
</tbody>
</table>

*EVLP, Ex vivo lung perfusion; PGD, primary graft dysfunction; ECLS, extracorporeal life support; ICU, intensive care unit.*
Survival

Survival
0 365 730 1095 1460
0
20
40
60
80
100
controls (n=253)
EVLP (n=50)
1             2            3             4
p=0.69

Years after LTx
Percent survival

Cypel et al. Experience with the first 50 ex vivo lung perfusions in clinical lung transplantation. JCTVS September 2012
Survival

Survival
0 365 730 1095 1460
0
20
40
60
80
100
controls (n=253)
EVLP BDD (n=28)
EVLP DCD (n=22)
p=0.71
1             2            3             4
Years after LTx
Percent survival

Years after LTx
0 1 2 3 4
0
20
40
60
80
100
controls (n=253)
EVLP BDD (n=28)
EVLP DCD (n=22)
p=0.71
EVLP Experience in Toronto

Assessed (n=77)

DBD (n=43)  DCD (n=34)

Transplants (n=34)  Transplants (n=27)

Utilization Rate of EVLP Lungs
61/77 = 80%
Total Lung Transplant and EVLP Activity /Year
1983-Sept 2012 (YTD)

- EVLP pre Tx
- LTx-no EVLP

<table>
<thead>
<tr>
<th>Year</th>
<th>No of Tx / yr</th>
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<td>1983</td>
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<td>2008</td>
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<td>2009</td>
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<tr>
<td>2010</td>
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<tr>
<td>2011</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td></td>
</tr>
</tbody>
</table>
1st Patient transplanted with Toronto EVLP system

2005
- Concept Development & Study Design
- Equipment Troubleshooting

2006
- 1st Animal Experiment

2007
- Human Trial Design: Researchers, Ethics board, patients

2008
- 1st Human Transplant

2010
- Completion of Trial and Health Canada Application
- Approved for clinical use

2012
- Reimbursement
- OHTAC
- MOH
- Health Canada
  - FDA pending
Current State of EVLP

• > 300 cases done North America and Europe
• 3 clinical trials (1 US and 2 Europe)
• XVIVO, Transmedics, Vivoline
<table>
<thead>
<tr>
<th></th>
<th>Toronto</th>
<th>Lund (Vivoline)</th>
<th>Organ Care System</th>
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<tbody>
<tr>
<td><strong>Perfusion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Target total</strong></td>
<td>40% cardiac output (1 h)</td>
<td>100% cardiac output (1 h)</td>
<td>2.5 L (15–30 min)</td>
</tr>
<tr>
<td><strong>Start rate</strong></td>
<td>150 mL/min</td>
<td>100 mL/min</td>
<td>200 mL/min</td>
</tr>
<tr>
<td><strong>Pulmonary arterial pressure</strong></td>
<td>&lt;15 mm Hg</td>
<td>&lt;20 mm Hg*</td>
<td>&lt;20 mm Hg</td>
</tr>
<tr>
<td><strong>Left atrial pressure</strong></td>
<td>3–5 mm Hg</td>
<td>0 mm Hg</td>
<td>0 mm Hg</td>
</tr>
<tr>
<td><strong>Pump</strong></td>
<td>Centrifugal</td>
<td>Roller</td>
<td>Pulsatile</td>
</tr>
<tr>
<td><strong>Perfusate</strong></td>
<td>2 L Steen solution</td>
<td>2 L Steen solution plus red blood cells (haematocrit 10%)</td>
<td>1.5 L Steen solution plus red blood cells (haematocrit 20%)</td>
</tr>
<tr>
<td><strong>Ventilation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mode</strong></td>
<td>Volume controlled</td>
<td>Volume controlled</td>
<td>Volume controlled</td>
</tr>
<tr>
<td><strong>Tidal volume</strong></td>
<td>7 mL/kg</td>
<td>5–7 mL/kg</td>
<td>6 mL/kg</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>7 bpm</td>
<td>20 bpm</td>
<td>10 bpm</td>
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<tr>
<td><strong>Positive end-expiratory pressure</strong></td>
<td>5 cm H\textsubscript{2}O</td>
<td>5 cm H\textsubscript{2}O</td>
<td>5 cm H\textsubscript{2}O</td>
</tr>
<tr>
<td><strong>Fraction of inspired oxygen</strong></td>
<td>21%</td>
<td>50%</td>
<td>21%</td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>Start ventilation</strong></td>
<td>32°C</td>
<td>32°C</td>
<td>32°C</td>
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<tr>
<td><strong>Start perfusion</strong></td>
<td>25°C</td>
<td>25°C</td>
<td>32°C</td>
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<tr>
<td><strong>Start evaluation</strong></td>
<td>37°C</td>
<td>37°C</td>
<td>37°C</td>
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<tr>
<td><strong>Perfusion time</strong></td>
<td>12 h</td>
<td>2 h</td>
<td>Duration of transport†</td>
</tr>
</tbody>
</table>

*Pulmonary arterial pressure of <15 mm Hg used in pigs. †Mean time of 5 h in pilot study (range 3–10).*

**Table 2: Ex-vivo lung perfusion protocols**
The Future of Ex Vivo Lung Perfusion: “Personalized Medicine for the Organ”

I. Advancing Ex vivo Therapies

II. Advancing Diagnostics – the "omics"
Ex vivo treatment opportunities
Donor lung injuries

1- Pulmonary Edema
2- Brain death associated inflammation
3- Infection, Pneumonia
4- Aspiration
5- Pulmonary emboli
6- Ischemia-reperfusion injury
7- Immunologic preparation
Advantages of ex vivo treatment

- Increased time for interventions
- Avoid systemic side effects
- Treatment is specific to the organ
- Prolonged half-life of drugs in perfusate
- Absence of systemic inflammatory milieu
- Opportunity for post-treatment re-assessment
EVLP as a platform for personalized medicine: Potential Early Wins

Lungs do not meet conventional criteria

Edema, Inflammation? Infection? Pulmonary embolism?

Pulmonary Physiology Imaging, Bronch, clinical diagnostics

Diagnose Treat Monitor response

Successful Transplant
Resolution of pulmonary edema during EVLP

Donor P/F 230

Recipient P/F 420

1h EVLP

3h EVLP
Beta-adrenergics further enhance AFC in human EVLP

Exogenous Epinephrine (Intratracheal)

Infection

• Large proportion of rejected human lungs
• EVLP is ideal
  • Super high doses of antibiotics can be administered without systemic effects
  • Prolonged half-life.

• Start with treatment of early infections or lung contralateral to established pneumonia
• Prolonged perfusion (>12h) might be required
Repairing Human Lungs with Presumed Infection

- 6 lungs rejected for suspicion of infection
- 12h normothermic EVLP with high doses of antibiotics
Ex Vivo Treatment of Infection

Ps Aeruginosa (n= 4)

S Aureus (n= 3)

St Maltophilia (n= 3)

Trichosporon (n= 3)

E Coli (n= 2)

Enterobacter (n= 1)

Control
Clinical Case:

Diagnosing and Treating a *Specific* Problem
Donor History

- Female, 49-yrs old, 187cm, 98kg
- Former-smoker, 10 pack-years, quit 10 years
- Lower limb pain and shortness of breath 2 days before admission
- Admission – right side paralysis - stroke
- Right mottled leg – acute arterial occlusion on right side – iliac-femoral embolectomy
- DVT on left popliteal vein – ultrasound
- Intracranial bleed
## Donor Assessment

<table>
<thead>
<tr>
<th>History</th>
<th>Thromboembolic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABG – P/F</td>
<td>266 mmHg</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>No infiltrates</td>
</tr>
<tr>
<td>Transthoracic ECHO RVSP</td>
<td>52 mmHg + RV dysfunction, consistent with massive PE</td>
</tr>
<tr>
<td>Bronchoscopy</td>
<td>Clear bilaterally</td>
</tr>
<tr>
<td>Intra-operative PAP</td>
<td>41/30 mmHg</td>
</tr>
<tr>
<td>Antegrade and Retrograde Flush</td>
<td>Macroscopic clots extracted bilaterally</td>
</tr>
</tbody>
</table>

**Concern:** Thrombotic/embolic history, Elevated RVSP, RV dysfunction, Heart turned down, PAH acute or chronic?
Surgical Extraction of Large Clots of Varying Age in Donor Lung PA
EVLP Assessment confirms the in vivo findings

- On initiation of EVLP: abnormal PA pressures even with low flows

Persistent hemodynamic impairment in the ex vivo organ

Apply similar diagnosis / treatment as in vivo treatment of massive PE

ALTEPLASE 20 mg (reduced clearance)
Significant improvement of Pulmonary Hemodynamics after treatment

**Diagnosis**

**Treatment**

**Response monitoring**

**Graph:**
- Comparison of sPAP and PVR over hours of EVLP with Alteplase treatment.
- sPAP: 30 mmHg at 0 hours, 20 mmHg at 6 hours.
- PVR: 1000 dynes.sec.cm⁻⁵ at 0 hours, 200 dynes.sec.cm⁻⁵ at 6 hours.
- PAP at 100% CO: 38 mmHg (before treatment), 25 mmHg (after treatment).
D-dimer and Evidence of Thrombolysis

Ex vivo treated lung with massive PE

11-fold increase
Pathology: Ex vivo lung biopsy, Quick Section pathologic Examination

No evidence of chronic vascular abnormalities
EX VIVO LUNG X-RAY

1hr after EVLP

3 hrs after EVLP
Donor vs. Recipient post-reperfusion

P/F 266 mmHg
RVSP 50 mmHg
Right Ventricular dysfunction
Intra-operative PAP 41/30 mmHg

P/F > 500 mmHg
PAP 28/9 mmHg
Extubation 12 hours
Engineering Superior Organs
Novel strategies for inflammation related ischemia reperfusion injury
Functional Repair of Human Donor Lungs by Ex Vivo IL-10 Gene Therapy

Delivery of IL-10 by EVLP Ad Gene Therapy to injured human donor lungs resulted in improved lung function.

AdIL-10 Gene Therapy Decreases Human Donor Lung Inflammation During EVLP

...and also reduced inflammatory cytokine expression

**IL-1β**

**IL-8**

**IL-10**

**TNF-α**

**IL-12p40**

**IL-6**

Recovery of alveolar epithelial cell tight junctions (ZO-1) after AdhIL-10 gene therapy in Human Lungs.

Allogeneic human mesenchymal stem cells for treatment of *E. coli* endotoxin-induced acute lung injury in the ex vivo perfused human lung

Jae W. Lee¹, Xiaohui Fang², Naveen Gupta³, Vladimir Serikov⁴, and Michael A. Matthay⁵,⁶,⁷

PNAS | September 22, 2009 | vol. 106 | no. 38 | 16357–16362
Mesenchymal Stem Cells (Soluble factors) Improve Endothelial permeability
Regeneration and orthotopic transplantation of a bioartificial lung

Harald C Ott¹, Ben Clippinger¹, Claudius Conrad¹, Christian Schuetz¹, Irina Pomerantseva¹, Laertis Ikonomou², Darrell Kotton² & Joseph P Vacanti¹

-RAT LUNG
-Perfusion decellularization with 0.1% SDS
-Recellularization with HUVECs (Human Umbilical Cord Endothelial Cells) through the vasculature; Basal Epithelial Cell Line (A549) through trachea to test biocompatibility of scaffold
-Recellularization with HUVECs and Rat fetal lung cells to test for gas-exchange

How to apply?

- Transplant Center - Centric Model
The Future of Transplantation…
The “Organ Repair Center”
Case Report

Successful Emergent Lung Transplantation After Remote Ex Vivo Perfusion Optimization and Transportation of Donor Lungs


Drug Administration; HCO, Bicarbonate; IRB, Institutional Review Board; ISHLT, International Society of Heart and Lung Transplantation; mmHg, Millimeters of Mercury; mmol/L, Millimolar; OPO, Organ Procurement Organization; pCO₂, Partial Pressure of Carbon Dioxide.
Bob Love’s Thank You Note:

“A staggering display of innovation, international collaboration, compassion and effective thinking that has left our administrators heads spinning…”
Current - EVLP report by email from Organ Perfusion Specialist (OPS)

This is the third hour report.
The lungs look stable. The compliance and oxygenation improved compared with the second hour. Bronch is similar to the first hour.

Pap 7/7/8
Pla 4/3/4
Pawp 16/15/14
Cdyn 62/66/71
Cstat 100/108/112
Delta P02 Pv-Pa 408/386.5/418.5

Vein P02 RUL 517.2/533/552
RLL 533.2/498.8/523.4
LUL 463/500/505
LLL 495.5/445/486.4
Attached is the xray.
Canada Operations

CLINICAL

RESEARCH & DEVELOPMENT

VANCOUVER

CALGARY

TORONTO
United States Operations

Optimized locations serve regional and national demand

**Numbers represent number of donors in each state**
CURRENT STANDARD PRACTICE IN ORGAN SELECTION AND MANAGEMENT

Donor Management → Organ Procurement → Cold Static Preservation → Transplantation (15%)

Decline 85% (Questionable organs are declined at procurement)

- Slows down death
- Unable to assess function

PGD rate = 30%
1st PARADIGM SHIFT IN ORGAN MANAGEMENT: Ex vivo evaluation

Donor Management

Organ Procurement

Cold Static Preservation

Ex vivo Evaluation

Decision

Transplantation (60%)

Decline (40%)
2nd Paradigm Shift in Organ Management: Ex vivo Organ Repair / Optimization

- Donor Management
- Organ Procurement
- Cold Preservation

Ex vivo Evaluation

Ex vivo Organ-Specific Injury Repair

Transplantation

Decision

Decline
Laboratories
Thanks!

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