Managing an Organ - New Therapies

Marcelo Cypel MD MSc
Canada Research Chair in Lung Transplantation
Surgical Director, ECLS program UHN
Assistant Professor of Surgery
Division of Thoracic Surgery
University of Toronto
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
First Lung Tx

First Double Lung Tx
Indications (TGH) N=1500

- Cystic Fibrosis: 22%
- ILD/IPF: 31%
- COPD/Emphysema: 33%
- Re-Tx: 3%
- Other: 3%
- PAH: 5%
- BAC: 1%
- Eisenmenger's: 3%
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
Low Utilization Rates

UNOS BD donors

BDD = 17%

UNOS DCD donors

DCD = 2%

www.unos.org.2011
Figure 1: Injuries to donor lungs in potential multiorgan donors

Clinical Problem - PGD
Reduction of cell metabolism by 95%
Normothermic Preservation

• 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
The Toronto Ex Vivo Lung Perfusion (EVLP) System is designed to mimic in vivo conditions for lung preservation and evaluation. The system includes a reservoir, leukocyte filter, pump, bridge, and an XVIVO chamber with lungs. The perfusion parameters are set to 40% CO, LAP 5mmHg, PAP 10-12mmHg, with ventilation at 7cc/kg, 7BPM, PEEP 5, and FiO₂ = 21%.

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

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

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
Lung Xray
Stable or Improved Ex vivo Function

Graph A: PaO\textsubscript{2}:FiO\textsubscript{2} Ratio (mm Hg)

- Donor
- Hours of EVLP: 1, 2, 3, 4

Graph B: Pulmonary Vascular Resistance (dynes·sec·cm\textsuperscript{-5})

- Hours of EVLP: 1, 2, 3, 4

Graph C: Dynamic Compliance (ml/cm of H\textsubscript{2}O)

Graph D: Peak Inspiratory Pressure (cm of H\textsubscript{2}O)
Early outcomes were similar in the 2 groups

<table>
<thead>
<tr>
<th>Table 2. Outcomes in the EVLP and Control Groups. *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End Point</strong></td>
</tr>
<tr>
<td>-------------</td>
</tr>
<tr>
<td><strong>Primary end point</strong>&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>PGD grade 2 or 3 at 72 hr (%)</td>
</tr>
<tr>
<td><strong>Secondary end points</strong>&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>PGD grade 2 or 3 at ICU arrival (%)</td>
</tr>
<tr>
<td>PGD grade 2 or 3 at 24 hr (%)</td>
</tr>
<tr>
<td>PGD grade 2 or 3 at 48 hr (%)</td>
</tr>
<tr>
<td>ECMO (%)</td>
</tr>
<tr>
<td>PaO&lt;sub&gt;2&lt;/sub&gt;:FiO&lt;sub&gt;2&lt;/sub&gt; on arrival in ICU (mm Hg)</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>Mechanical ventilation after transplantation (days)</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>ICU stay after transplantation (days)</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>Hospital stay after transplantation (days)</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Range</td>
</tr>
</tbody>
</table>

*Data are counts, except for PGD grade 2 or 3 at 72 hr, which are percentages. Values are shown as counts, except for PaO<sub>2</sub>:FiO<sub>2</sub>, mechanical ventilation, ICU stay, and hospital stay, which are shown as median and range. 

<sup*f</sup>P values are for comparisons between EVLP and control lungs.
### 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>
</thead>
<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>.30</td>
</tr>
<tr>
<td>Median</td>
<td>2</td>
<td>2.2</td>
<td></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 intervention (%)</td>
<td>4</td>
<td>4</td>
<td>1.00</td>
</tr>
</tbody>
</table>

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

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

Survival rates over time for different groups:
- Controls (n=253)
- EVLP BDD (n=28)
- EVLP DCD (n=22)

Years after LTx vs Percent survival

p=0.71
EVLP Experience in Toronto

Assessed (n=105)

Transplants (n=84)

Transplants (n=21)

Utilization Rate of EVLP Lungs
84/105 = 80%
EVLPP vs. Lung Tx Activities / Year
2008–Oct 2013 (YTD)
Current State of EVLP

• > 300 cases done North America and Europe
• 3 clinical trials (1 US and 2 Europe)
• XVIVO, Transmedics, Vivoline
Engineering Superior Organs
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
Resolution of pulmonary edema during EVLP

Donor P/F 230

Recipient P/F 420

1h EVLP

3h EVLP
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

### Pneumonia - Mean Delta pO2 (FiO2 1)

![Graph showing mean delta pO2 over time]

- Y-axis: Mean Delta pO2 (FiO2 1)
- X-axis: Time (1, 3, 6, 9, 12 hours)

- Values range from approximately 200 to 600
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)
Clinical Case:

Diagnosing and Treating a *Specific* Problem
Surgical Extraction of Large Clots of Varying Age in Donor Lung PA

Right Pulmonary Artery
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

Alteplase

sPAP mmHg vs. hours EVLP

PVR dynssec.cm⁻¹

PAP at 100% CO

diagnosis
treatment
Response monitoring
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
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.

PaO$_2$/FiO$_2$ vs. Change from Baseline

PVR vs. Change from Baseline

EVLP/AdIL-10 vs. EVLP
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. Leea, Xiaohui Fangb, Naveen Guptac, Vladimir Serikovd, and Michael A. Matthaya,b,c

PNAS | September 22, 2009 | vol. 106 | no. 38 | 16357–16362
Organ Repair Center (Perfusion)

- Transplant
- Transplant
- Transplant
- Transplant
- Transplant
The Future of Transplantation…
The “Organ Repair Center”

Lung

Heart

Liver

Kidney
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
Exterior Rendering

Spring Street Façade/Orange
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
Thank you!

marcelo.cypel@uhn.ca
www.dotscanada.ca