Ex vivo Organ Repair

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DISCLOSURE

- XVIVO Perfusion – Research support and clinical trial
- Founding Partner:
  - Perfusix Canada Inc.
  - Perfusix USA Inc.
  - XOR Labs Toronto Inc.
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%
Low Utilization Rates

BDD = 17%

DCD = 2%


**Figure 1: Injuries to donor lungs in potential multiorgan donors**

Clinical Problem - PGD
First Successful Lung Transplantation in the World
Toronto General Hospital 1983
G Pearson, J Cooper, A Patterson, T Todd
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-

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

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

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.
Early outcomes were similar in the 2 groups.

Table 2. Outcomes in the EVLP and Control 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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Donors without a Heartbeat (N = 9)</td>
<td>Brain-Dead Donors (N = 11)</td>
<td></td>
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<tr>
<td><strong>Primary end point§</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PGD grade 2 or 3 at 72 hr (%)</td>
<td>11</td>
<td>18</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td><strong>Secondary end points§</strong></td>
<td></td>
<td></td>
<td></td>
<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>36</td>
<td>21 (3 to 39)</td>
</tr>
<tr>
<td>PGD grade 2 or 3 at 48 hr (%)</td>
<td>33</td>
<td>27</td>
<td>35</td>
<td>5 (—17 to 27)</td>
</tr>
<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>420</td>
<td>423</td>
<td>422</td>
<td>372</td>
</tr>
<tr>
<td>Median</td>
<td>85–518</td>
<td>86–538</td>
<td>85–538</td>
<td>49–591</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation after transplantation (days)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Median</td>
<td>1–27</td>
<td>1–101</td>
<td>1–101</td>
<td>1–43</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU stay after transplantation (days)</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Median</td>
<td>1–34</td>
<td>1–101</td>
<td>1–101</td>
<td>1–103</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital stay after transplantation (days)</td>
<td>19</td>
<td>34</td>
<td>23</td>
<td>27</td>
</tr>
<tr>
<td>Median</td>
<td>7–54</td>
<td>11–101</td>
<td>7–101</td>
<td>9–156</td>
</tr>
<tr>
<td>Range</td>
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</table>
What is the impact of EVLP to our program?
Clinical Experience with EVLP at UHN

Conversion Rate = 78%

213 EVLPs
166LTx
47 declined
Ontario Donors vs. LTx/Year
1991-Oct 22, 2015 (YTD)
% of Transplants are from EVLP lungs
Outcomes with Clinical EVLP

K-M Survival Plot; EVLP (Yes/NO); Redo Excluded; N=699 (143+556)

p=0.956 (Log-Rank)
Freedom from CLAD
(EVLP of high risk NDDs)

P = 0.03

No. at risk
EVLP  25  24  18  10  6
Control  305  252  156  91  38

Tikkanen / Singer, JHLT 2015
How does EVLP rescue more lungs?
1) Improvement in Lung Assessment
DCD
Lung Transplantation With Donation After Circulatory Determination of Death Donors and the Impact of Ex Vivo Lung Perfusion


Jan 2007 to Oct 2013

62 DCD lung transplants

30 no EVLP transplants

3 ECLS cases

27 no EVLP transplants

32 EVLP transplants

4 ECLS cases

28 EVLP transplants

Figure 4
## Donor, Recipient and Early Outcome

<table>
<thead>
<tr>
<th>variable</th>
<th>No EVLP</th>
<th>EVLP</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor Age</td>
<td>39 ± 19</td>
<td>45 ± 13</td>
<td>0.16</td>
</tr>
<tr>
<td>Donor +ve culture</td>
<td>17 (62%)</td>
<td>23 (82%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Donor P/F ratio</td>
<td>429 ± 66</td>
<td>380 ± 103</td>
<td>0.04</td>
</tr>
<tr>
<td>Diagnosis IPF/PH</td>
<td>12 (44%)</td>
<td>13 (46%)</td>
<td>1</td>
</tr>
<tr>
<td>Age</td>
<td>50 ± 16</td>
<td>52 ± 13</td>
<td>0.73</td>
</tr>
<tr>
<td>BMI</td>
<td>23 ± 4</td>
<td>23 ± 3</td>
<td>0.99</td>
</tr>
<tr>
<td>Bilateral</td>
<td>21 (77%)</td>
<td>21 (75%)</td>
<td>1</td>
</tr>
<tr>
<td>Time on MV</td>
<td>3 (1-13)</td>
<td>2 (1-3)</td>
<td>0.05</td>
</tr>
<tr>
<td>ICU Stay</td>
<td>6 (2-17)</td>
<td>3 (2-7)</td>
<td>0.07</td>
</tr>
<tr>
<td>Hospital Stay</td>
<td>23 (16-41)</td>
<td>18 (14-22)</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Successful lung transplantation from a donation after cardiocirculatory death donor taking more than 120 minutes to cardiac arrest after withdrawal of life support therapies.
2) Treatment Strategies
Ex vivo treatment opportunities - Donor lung injuries

Figure 1: Injuries to donor lungs in potential multiorgan donors
Treatment Strategies

- Perfusion
- Gene Therapy
- Cell Therapy
- Immuno-cloaking
- Inhaled Gases
- Drugs
- Biological
Resolution of pulmonary edema during EVLP

Donor P/F 230

Recipient P/F 420

1h EVLP

3h EVLP
Case Report # 2

<table>
<thead>
<tr>
<th>History</th>
<th>Thromboembolic disease</th>
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<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>Antegradate 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?

**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
- PVR dynssec/cm²

Response monitoring

diagnosis

treatment

PAP at 100% CO
38 mmHg
25 mmHg

University Health Network
D-dimer and Evidence of Thrombolysis

Knecht et al. PE + fibrinolysis
Thromb Res 1992

d-dimer PE

Brenner et al. MI + fibrinolysis
Circulation 1998

d-dimer MI

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
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
Ongoing EVLP treatment projects

- **Antibiotics** – human and animal models
- **Surfactant + lung lavage** – human and animal models
- **CO + H2S** inhaled gas
- **Anti-cell death** treatment
- **Immuno-cloaking**
- **Stem Cell**
HEP C
(>400 donors in USA/Year)

Donor
60 years old, male
Stroke – intracranial hemorrhage
Last ABG PaO2 179 mmHg
Hepatitis C

Recipient
Male, 44 years old
Pulmonary Fibrosis
Rapid deteriorating list
Perfusate viral load

HCV viral load (IU/ml)

Hours of EVLP
Tissue viral load

HCV viral load (IU/ml) vs. Hours of EVLP

Hours of EVLP
Our family would just like to say Thank you! once again for taking such good care of Andrew. He has just had his 3 month check up and there are no concerns 😊 He is doing so well. We are returning home to New Brunswick very soon. God Bless you!

Love
Andrew + Lisa Currie + family
Clinical EVLP projects 2015

- IL-10 Gene Therapy
  - Phase I clinical trial (n=12)

- Non-Perfused Organ Donors (n=10)
## NPOD SCREENING TOOL

Fax to TGLN when complete - **416-214-7797**

*This document does not get attached to the chart. See reverse for additional information on the study.*

### DATE __________________ LOCATION ____________

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**The patient is under 65 years of age.**

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**The arrest was witnessed or was the patient last seen alive less than 1 hour prior to arrest.**

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**Death was declared in the last thirty minutes.**

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**The MRP or internist feels that this case may not need coroner involvement.***

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**The smoking history is unknown or less than 20 pack-years**

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**There is no known or confirmed history of COPD.**

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**There is no known cancer in the past five years.**

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**The cause of death is not felt to be related to asthma.**

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**Estimated Time of Arrest ________________ Time of Death ________________**

**Estimated Duration of Resuscitation – Time Start: ___________ Duration _______**
The Future of Transplantation…
The “Organ Repair Center”

- Lung
- Heart
- Liver
- Kidney
Commercial Devices for Ex Vivo Lung Perfusion

“The Organ Hub”
Perfusix-1 (PX1, Lung Bioengineering Inc.)