Optimizing the Donor Lung with EVLP

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Disclosure

• Founding Partner:
  • Perfusix Canada Inc.
  • Perfusix USA Inc. (Lung Bioengineering /UT)
  • XOR Labs Toronto Inc.
• XVIVO Perfusion – Research support and clinical trial
• United Therapeutics – Consultant
• Xenios/Fresenius – Research support and investor in XOR
• Gilead Sciences – Research Support
Low Utilization Rates of Donor Lungs

2015: 20% NDD and 2% DCD

www.unos.org
Itiorgan donors

Clinical Problem – PGD 3


Cold Static Preservation
Cold Preservation

• At 4°C cellular metabolism is reduced to about 5% of normal
• Protective – injurious processes (dying) slowed
• Problem:
  • Injured organs cannot be actively improved/repaired
Normothermic Ex vivo Lung Perfusion

- Time to accurately assess, diagnose (improve utilization)
- Option to treat, recover, repair (targeted)
- Opportunity to reassess → confirm results of treatment
1) Perfusate flow: low vs high
2) Pump flow: continuous vs pulsatile
3) Perfusate composition: acellular vs cellular (blood)
4) Perfusate temperature: cold, 25°C or 37°C
5) Left Atrial Pressure: 0 vs 5 mmHg
6) Ventilation Strategy: low Vt vs high Vt, PEEP?
7) Supply of CO₂ to perfusate: required or not
Gas for Deoxygenation
86% N₂, 8% CO₂, 6% O₂

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

Leukocyte filter
Membrane (De)oxyg enator
Bridge

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

DEVELOPMENT OF A STABLE AND RELIABLE EX VIVO LUNG PERFUSION TECHNIQUE

Normothermic Ex Vivo Lung Perfusion in Clinical Lung Transplantation

Marcelo Cypel, M.D., Jonathan C. Yeung, M.D., Mingyao Liu, M.D., Masaki Arraku, 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.
Donor for 1st Clinical EVLP (October 2008)

- 20 yo male
- MVA trauma
- 21 units RBC transfusion
- PaO$_2$ range 230-260 mmHg
- CXR – pulmonary edema
- Bronchoscopy – Bloody secretions
EVLP Xrays

1h EVLP
P/F 250mmHg

3h EVLP
P/F 460mmHg
Recipient CXR on ICU Arrival
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>Donors without a HeartBeat (N=9)</th>
<th>Brain-Dead Donors (N=11)</th>
<th>Total (N=20)</th>
<th>Absolute Difference†</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EVLP Lungs (N=20)</td>
<td></td>
<td></td>
<td>percentage points (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Primary end point§</td>
<td>11</td>
<td>18</td>
<td>15 (N=20)</td>
<td>30 (N=20)</td>
<td>0.11</td>
</tr>
<tr>
<td>PGD grade 2 or 3 at 72 hr (%)</td>
<td>33</td>
<td>11</td>
<td>25 (N=20)</td>
<td>30 (N=20)</td>
<td>0.30</td>
</tr>
<tr>
<td>PGD grade 2 or 3 at ICU arrival (%)</td>
<td>11</td>
<td>18</td>
<td>15 (N=20)</td>
<td>30 (N=20)</td>
<td>0.07</td>
</tr>
<tr>
<td>PGD grade 2 or 3 at 24 hr (%)</td>
<td>33</td>
<td>33</td>
<td>15 (N=11)</td>
<td>30 (N=11)</td>
<td>0.46</td>
</tr>
<tr>
<td>PGD grade 2 or 3 at 48 hr (%)</td>
<td>1</td>
<td>27</td>
<td>15 (N=11)</td>
<td>30 (N=11)</td>
<td>0.37</td>
</tr>
<tr>
<td>ECMO (%)</td>
<td>2</td>
<td>18</td>
<td>15 (N=20)</td>
<td>30 (N=20)</td>
<td>0.37</td>
</tr>
<tr>
<td>PaO2/FiO2 on arrival in ICU (mm Hg)</td>
<td>420</td>
<td>423</td>
<td>422 (N=20)</td>
<td>372 (N=20)</td>
<td>0.51</td>
</tr>
<tr>
<td>Median</td>
<td>85–518</td>
<td>86–538</td>
<td>85–538</td>
<td>49–591</td>
<td>0.15</td>
</tr>
<tr>
<td>Range</td>
<td>2</td>
<td>2</td>
<td>2 (N=20)</td>
<td>2 (N=20)</td>
<td>0.15</td>
</tr>
<tr>
<td>Mechanical ventilation after transplantation (days)</td>
<td>2</td>
<td>1–27</td>
<td>2 (N=11)</td>
<td>2 (N=11)</td>
<td>0.15</td>
</tr>
<tr>
<td>ICU stay after transplantation (days)</td>
<td>1–27</td>
<td>1–101</td>
<td>2 (N=11)</td>
<td>2 (N=11)</td>
<td>0.15</td>
</tr>
<tr>
<td>Hospital stay after transplantation (days)</td>
<td>19</td>
<td>34</td>
<td>23 (N=20)</td>
<td>27 (N=20)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

NEJM, April 14th 2011
EVLMP for high risk donor lungs is safe

133 EVLPs vs. 133 matched controls

<table>
<thead>
<tr>
<th>Time (Years)</th>
<th>Surviving probability (%)</th>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EVLP: No</td>
<td>EVLP: Yes</td>
</tr>
<tr>
<td>0</td>
<td>100</td>
<td>133</td>
</tr>
<tr>
<td>1</td>
<td>97</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>94</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>91</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>87</td>
<td>26</td>
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<tr>
<td>5</td>
<td>83</td>
<td>14</td>
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<tr>
<td>6</td>
<td>79</td>
<td>10</td>
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<td>7</td>
<td>75</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>71</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>67</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>63</td>
<td>0</td>
</tr>
</tbody>
</table>

Yeung, J. JHLT 2016
Indications for EVLP

1) “Unusable” Donor: EVLP treatment
2) Questionable Donor
3) Standard cDCD: EVLP testing
4) Extended cDCD
5) Logistics (safe prolongation of preservation period)
“Unusable Lung”

1) Massive Edema
2) Pneumonia
3) Aspiration
4) Massive Pulmonary Emboli
5) Chronic Virus Infection (i.e Hep C)
6) Long Warm Ischemia in Controlled and Uncontrolled DCD
Treatment Strategies

- Perfusion
- Gene Therapy
- Cell Therapy
- Immuno-cloaking
- Inhaled Gases
- Drugs
- Biological
Pulmonary Edema
Resolution of pulmonary edema

Donor P/F 230

Recipient P/F 420

1h EVLP

3h EVLP
9 years alive
Adjunct Therapies to Improve Edema

• Proper perfusion/ventilation strategies
  (Linacre V et al; Importance of Left Atrium Strategy in EVLP; JHLT 2016)

• Use of drugs to stimulate AFC


Pneumonia
Infection

• Large proportion of rejected human lungs

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

• Prolonged perfusion (>12h) might be required
Significant decrease of bacteria during EVLP

Nakajima et al. Am J Transplant 2016 Apr;16(4):1229-37
Treatment of Infection is Associated with Improved Lung Function

Nakajima et al. Am J Transplant 2016 Apr;16(4):1229-37
Aspiration
Aspiration

- Very common cause for donor lung decline
- More prevalent in DCDs after WLST
Superior post-transplant function with lung lavage followed by surfactant replacement

Nakajima, JHLT, 2017 May;36 (5):577-585
Pulmonary Emboli
Case Report

<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?

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

**Alteplase**

- **sPAP mmHg**
- **PVR dynes.sec.cm⁻⁵**

**Response monitoring**

**Diagnosis**

**Treatment**
Pathology: Ex vivo lung biopsy, Quick Section

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
Donor Lungs with Infectious Diseases: Hep C

- 800-1000 actual donors/year in North America
- Young donors, good lungs
- Lungs are not offered for transplant due to ~ 100% chance of transmission for RNA+ donors
Case Report

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

Recipient
Male, 44 years old
Pulmonary Fibrosis
Transplant in 2013
Admitted to ICU: Severe hypoxemia P/F 48 mmHg
Successful Lung Transplantation From Hepatitis C Positive Donor to Seronegative Recipient

EVLP Effect

Light-based therapy (UVC) during EVLP
UVC is effective to eradicate HCV infectivity and replication

Results

**qPCR from RealTime PCR**

- **Infectivity log TCID50/mL**
  - Time (min): 0 15 30 45 60 90 120 150 180
  - Infectivity log TCID50/mL:
    - UVC: 0 1 2 3 4 5
    - Control: 0 1 2 3 4 5

- **Loss of infectivity**

**Inactivation of HCV**

- **IU/mL**
  - Time (min): 0 15 30 45 60 90 120 150 180
  - IU/mL:
    - UVC: 0 500000 1000000 1500000
    - Control: 0 500000 1000000 1500000

- **Loss of infectivity**
Inflammation
Functional Repair of Human Donor Lungs by IL-10 Gene Therapy

Marcelo Cypel,1,2 Mingyao Liu,1,2 Matt Rubacha,1 Jonathan C. Yeung,1,2 Shin Hirayama,1,2 Masaki Anraku,1,2 Masaaki Sato,1,2 Jeffrey Medin,3 Beverly L. Davidson,4 Marc de Perrot,1,2 Thomas K. Waddell,1,2 Arthur S. Slutsky,5,6 Shaf Keshavjee1,2*

A
Lung tissue

***

B

EVL (37°C) CSP (4°C)

EVL
Delivery of IL-10 by EVLP Ad Gene Therapy to injured human donor lungs resulted in improved lung function.
**IL-1ra change from BL in lung tissue (pg/mg)**

- **P = 0.0317**

**IL-8 in perfusate (pg/mL)**

- **P = 0.0455**

(Repeated ANOVA & Bonferroni post-tests)
EVLP in 2018

• Great tool to “test” quality of donor lungs: NDD and DCD

• Allow simple treatment strategies (i.e. drugs) to improve most common causes of donor lung injury

• Significantly prolong preservation times
EVLP in Future…..

Platform for major advances in organ transplantation including:

• Cell and Genetic modification: Gene Therapy, MSC, T regs…
• Immuno-cloaking
• Organ modification in Xenotransplantation
• Platform for patient own organ repair
• Bioreactor for Decel/Recel