Strategies for Donor Lung Repair

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No disclosure
Lung Transplantation is Limited by the Availability of Donor Organs

Disparity Between Transplants Performed and Waiting List

CIHI, 2011
Low Utilization Rates Exacerbates Low Donor Availability

BDD=17%

DCD=2%

www.unos.org.2011
Donor Lungs are Particularly Susceptible to Injury

- Ventilator-associated lung injury
- Ischaemic times
- Excess fluid
- Aspiration or pneumonia
- Local ischaemia (induced by vasopressors and cold flush)
- Brain death
- Thrombosis
- Activation of inflammatory cascade
- Primary graft dysfunction after transplantation

*Figure 1: Injuries to donor lungs in potential multiorgan donors*
Results in Primary Graft Dysfunction
Worldwide 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 to avoid PGD)

- Slows down death
- Unable to assess function

PGD rate = 30%

Decision
Worldwide Current Standard Practice in Organ Selection and Management

Donor Management

Decline 85%
(Questionable organs are declined at procurement to

How can we do this better?

Cold Static Preservation

- Slows down death
- Unable to assess function

Transplantation (15%)

PGD rate = 30%
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
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%

Video
DEVELOPMENT OF A STABLE AND RELIABLE EX VIVO LUNG PERFUSION TECHNIQUE

Hypothermic vs Normothermic Preservation

**Hypothermic**
- Slows metabolism/death
- Lungs are Static
- Cannot evaluate
- Cannot treat

**Normothermic**
- Supports metabolism
- Lungs continue to Function
- Potential to evaluate
- Potential to treat
PARADIGM SHIFT IN LUNG TRANSPLANTATION: Ex vivo evaluation

Decision

Donor Management

Organ Procurement

Cold Static Preservation

Ex vivo Evaluation

Brain-Death Physiology Evaluate at one time point

Evaluation in controlled setting Evaluate over hours

Transplantation

Decline
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>
<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>Donors without a Heartbeat (N=9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain-Dead Donors (N=11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (N=20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary end point§</strong></td>
<td></td>
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</tr>
<tr>
<td>PGD grade 2 or 3 at 72 hr (%)</td>
<td>11</td>
<td>18</td>
<td>35</td>
<td>30</td>
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<tr>
<td><strong>Secondary end points§</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<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>
</tr>
<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>
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<tr>
<td>PaO₂:FiO₂ on arrival in ICU (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td>0.51</td>
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<tr>
<td>Median</td>
<td>420</td>
<td>423</td>
<td>422</td>
<td>372</td>
</tr>
<tr>
<td>Range</td>
<td>85–518</td>
<td>86–538</td>
<td>85–538</td>
<td>49–591</td>
</tr>
<tr>
<td>Mechanical ventilation after transplantation (days)</td>
<td></td>
<td></td>
<td></td>
<td>0.15</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>0.68</td>
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<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>0.39</td>
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<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>
Ontario Donors vs. LTx/Year
1991-Oct 22, 2015 (YTD)

Number of Donors

Number of LTx

Year

LTx/Year

Deceased Donors (ON)

28%
% of Transplants are from EVLP lungs
Outcomes with Clinical EVLP

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

\[ p = 0.956 \text{ (Log-Rank)} \]
Freedom from CLAD
(EVLP of high risk NDDs)

P = 0.03

No. at risk

<table>
<thead>
<tr>
<th>EVLP</th>
<th>Control</th>
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<tbody>
<tr>
<td>25</td>
<td>305</td>
</tr>
<tr>
<td>24</td>
<td>252</td>
</tr>
<tr>
<td>18</td>
<td>156</td>
</tr>
<tr>
<td>10</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td>38</td>
</tr>
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</table>

Tikkanen / Singer, JHLT 2015
PARADIGM SHIFT IN ORGAN MANAGEMENT:
2. Ex vivo Organ Repair

Donor Management
Organ Procurement
Cold Static Preservation

Ex vivo Evaluation
Ex vivo Repair Strategy
Transplantation

Decision

Decline
Treatment Strategies
Donor lung injuries = Ex vivo treatment opportunities

**Perfusion**
- Excess fluid
- Local ischaemia (and cold flush)
- Thrombosis

**Inhaled Gases**
- Ventilator-associated lung injury
- Aspiration or pneumonia
- Brain death

**Cell Therapy**

**Gene Therapy**

**Immunomodulation**

**Drugs**

**Biological**

*Figure 1: Injuries to donor lungs in potential multiorgan donors*
Donor lung injuries = Ex vivo treatment opportunities

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

Donor P/F 230

Recipient P/F 420

1h EVLP

3h EVLP
Donor lung injuries = Ex vivo treatment opportunities

- Gene Therapy
- Cell Therapy
- Immunomodulation
- Perfusion
- Inhaled Gases
- Drugs
- Biological
**Ex vivo treatment of donor thromboembolic disease**

<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?

EVLPP 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 dynessec.cm⁻⁵

**Response monitoring**

- diagnosis
- treatment
D-dimer and Evidence of Thrombolysis

Knecht et al. PE + fibrinolysis
Thromb Res 1992

Brenner et al. MI + fibrinolysis
Circulation 1998

Ex vivo treated lung with massive PE

11-fold increase

18-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
Drugs
Perfusion
Gene Therapy
Cell Therapy
Immunomodulation
Inhaled Gases
Biological
Drugs
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)

Hours of EVLP
Outcomes

- DC home POD 28

- Eradication of HCV virus using anti-viral drugs post-op
  - Undetectable viral levels
Targeting NFkB Function: IL-10

IL-10

JAK/STAT Pathway
IL-10 Gene Therapy reduces ischemia-reperfusion injury in models of lung transplantation

Rat Model: IT AdhIL-10 to donor 12h prior to retrieval

Pig Model: IT AdhIL-10 to donor 12h prior to retrieval

(Fischer et al. *Human Gene Therapy* 12:1513–1526)

Current Barriers to Adoption of Clinical Gene Therapy

• Biological
  • Vector-associated inflammation

• Logistics
  • Gene transfer at donor hospital

• Timing
  • 6-9 hours of wait time in a brain-dead donor for transgene expression
Ex vivo Gene Delivery Resulted in Effective Gene Transduction

Yeung et al
EVLP Gene Therapy Reduces Vector-Associated Inflammation

Ex vivo AdGFP

In vivo AdGFP

Yeung et al
Ex vivo Gene Therapy is Superior to In vivo

• Biological
  • Vector-associated inflammation

• Logistics
  • Gene transfer at donor hospital

• Timing
  • 6-9 hours of wait time in a brain-dead donor for transgene expression
Ex vivo Gene Therapy is Superior to In vivo

• Biological
  • Reduced Vector-associated inflammation

• Logistics
  • Gene transfer at recipient/base hospital

• Timing
  • 6-9 hours of wait time ex vivo for transgene expression
Post-Transplant Lung Function at day 7 is better in AdhIL-10 group

* $p < 0.05$
There is a trend towards lesser A grade acute rejection in AdhIL-10 group.

**Acute Rejection**

<table>
<thead>
<tr>
<th>Group</th>
<th>A grade</th>
<th>B grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVLP-only</td>
<td>3.5</td>
<td>1.2</td>
</tr>
<tr>
<td>AdhIL-10</td>
<td>2.3</td>
<td>0.9</td>
</tr>
</tbody>
</table>

\( p = 0.06 \)

**Bronchial Inflammation**

<table>
<thead>
<tr>
<th>Group</th>
<th>A grade</th>
<th>B grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVLP-only</td>
<td>2.8</td>
<td>0.6</td>
</tr>
<tr>
<td>AdhIL-10</td>
<td>2.0</td>
<td>0.5</td>
</tr>
</tbody>
</table>

\( p = 0.24 \)

Machuca et al
Future Direction

• IL-10 Gene Therapy 2016
  - Phase I clinical trial (n=12)
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**