Ex-Vivo Lung Perfusion

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Surgical Director, Lung Transplant Program
Conflicts of Interest

• Local PI in NOVEL Lung Trial Supported by Vitrolife Inc., Sweden.
Learning Objectives

- Understand the demographics of lung transplantation in regards to donor limitations
- Understand the limitations of the donor lung under current conditions
- Develop an understanding of the expanded potential of EVLP to evaluate the donor organ
- Review progress on the U.S. Experience with EVLP
Current Challenges in Lung Transplantation

- Donor Organ Shortage
- Primary Graft Dysfunction
- Chronic Rejection/Bronchiolitis Obliterans
Donor Organ Shortage

- 15% - 25% of MOD suitable lungs
- increasing donor age
- increased waiting time
- waiting list mortality 10% - 30%
Pulmonary Graft Injury

Incidence
10 – 25 %

Mortality
2 – 3 %

brain death
cold ischemia

warm ischemia
reperfusion
Mortality post-lung transplant

Poor predictors of graft function

<table>
<thead>
<tr>
<th>CAUSE OF DEATH</th>
<th>0-30 Days (N = 1,427)</th>
<th>31 Days – 1 Year (N = 2,128)</th>
<th>&gt;1 Year – 3 Years (N = 1,827)</th>
<th>&gt;3 Years – 5 Years (N = 1,063)</th>
<th>&gt;5 Years – 10 Years (N = 1,097)</th>
<th>&gt;10 Years (N = 148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRONCHIOLITIS</td>
<td>6 (0.4%)</td>
<td>103 (4.8%)</td>
<td>505 (27.6%)</td>
<td>319 (30.0%)</td>
<td>295 (26.9%)</td>
<td>35 (23.6%)</td>
</tr>
<tr>
<td>ACUTE REJECTION</td>
<td>67 (4.7%)</td>
<td>43 (2.0%)</td>
<td>34 (1.9%)</td>
<td>9 (0.8%)</td>
<td>8 (0.7%)</td>
<td>0</td>
</tr>
<tr>
<td>LYMPHOMA</td>
<td>1 (0.1%)</td>
<td>55 (2.6%)</td>
<td>39 (2.1%)</td>
<td>17 (1.6%)</td>
<td>31 (2.8%)</td>
<td>7 (4.7%)</td>
</tr>
<tr>
<td>MALIGNANCY, OTHER</td>
<td>1 (0.1%)</td>
<td>55 (2.6%)</td>
<td>104 (5.7%)</td>
<td>83 (7.8%)</td>
<td>94 (8.6%)</td>
<td>11 (7.4%)</td>
</tr>
<tr>
<td>CMV</td>
<td>0</td>
<td>72 (3.4%)</td>
<td>22 (1.2%)</td>
<td>4 (0.4%)</td>
<td>3 (0.3%)</td>
<td>0</td>
</tr>
<tr>
<td>INFECTION, NON-CMV</td>
<td>290 (20.3%)</td>
<td>775 (36.4%)</td>
<td>439 (24.0%)</td>
<td>195 (18.3%)</td>
<td>198 (18.0%)</td>
<td>24 (16.2%)</td>
</tr>
<tr>
<td>GRAFT FAILURE</td>
<td>404 (28.3%)</td>
<td>409 (19.2%)</td>
<td>335 (18.3%)</td>
<td>200 (18.8%)</td>
<td>197 (18.0%)</td>
<td>34 (23.0%)</td>
</tr>
<tr>
<td>CARDIOVASCULAR</td>
<td>154 (10.8%)</td>
<td>89 (4.2%)</td>
<td>57 (3.1%)</td>
<td>51 (4.8%)</td>
<td>57 (5.2%)</td>
<td>9 (6.1%)</td>
</tr>
<tr>
<td>TECHNICAL</td>
<td>117 (8.2%)</td>
<td>58 (2.7%)</td>
<td>13 (0.7%)</td>
<td>3 (0.3%)</td>
<td>3 (0.3%)</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>OTHER</td>
<td>387 (27.1%)</td>
<td>469 (22.0%)</td>
<td>279 (15.3%)</td>
<td>185 (17.1%)</td>
<td>211 (19.2%)</td>
<td>27 (18.2%)</td>
</tr>
</tbody>
</table>

J Heart Lung Transplant 2007; 26: 782-95
Current donor lung assessment?

- **Functional performance**
  Gas exchange (O\textsubscript{2} challenge: PO\textsubscript{2} / FiO\textsubscript{2} > 300 mm Hg)

- **Radiographic appearance**
  Chest x-ray, CT chest

- **Bronchoscopic findings**
  Secretions, airway inflammation

- **Visual findings**
  Nodules, infiltrates, contusion, edema

*Primitive !!*
## Leading Causes of Non-recovery

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac arrest</td>
<td>77</td>
<td>92</td>
<td>47</td>
<td>65</td>
<td>98</td>
</tr>
<tr>
<td>Organ unsatisfactory*</td>
<td>594</td>
<td>618</td>
<td>734</td>
<td>744</td>
<td>819</td>
</tr>
<tr>
<td>Poor organ function</td>
<td>6,461</td>
<td>6,570</td>
<td>6,506</td>
<td>6,103</td>
<td>6,313</td>
</tr>
<tr>
<td>Donor medical/social history</td>
<td>874</td>
<td>702</td>
<td>901</td>
<td>1,015</td>
<td>865</td>
</tr>
<tr>
<td>Biopsy findings</td>
<td>3</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Positive hepatitis/HIV/HTLV-1</td>
<td>436</td>
<td>340</td>
<td>344</td>
<td>294</td>
<td>246</td>
</tr>
<tr>
<td>No recipient found*</td>
<td>967</td>
<td>1,240</td>
<td>1,144</td>
<td>1,119</td>
<td>1,223</td>
</tr>
<tr>
<td>Other</td>
<td>1,329</td>
<td>1,269</td>
<td>1,152</td>
<td>1,103</td>
<td>1,165</td>
</tr>
</tbody>
</table>

* UNOS-OPTN 2012.
Rejected Lungs

Assessment of lungs rejected for transplantation and implications for donor selection

Lorraine B Ware, Yibing Wang, Xiaohui Fang, Martha Warnock, Tsutomu Sakuma, Timothy S Hall, Michael A Matthay

Lancet 2002; 360: 619-20
Ex-Vivo Lung Perfusion (EVLP) Overview

- Historical Perspective
- Technique
- Physiology
- Future Applications
Ex-vivo evaluation of donor lungs

History


Ex vivo evaluation of stored lungs.

Jirsch DW, Fisk RL, Couves CM.


Autoperfusion of the heart and lungs for preservation during distant procurement.

Hardesty RL, Griffith BP.

A modified autoperfusing Starling preparation was used to provide pulmonary and coronary blood flow to extend the period of preservation for heart-lung transplantation. Twenty successful donations were achieved, 14 performed, and both the heart and lungs were well preserved in 14 of them. In four recipients it was not possible to assess the adequacy of preservation. In one recipient the preservation was not satisfactory, and in another the selection of the donor was responsible for poor cardiac function. Ten patients are alive who would not be were it not for this technique.
Ex-vivo evaluation of donor lungs

History

Ex Vivo Evaluation of Nonacceptable Donor Lungs
Per Wierup, MD, PhD, Åsa Haraldsson, MD, PhD, Folke Nilsson, MD, PhD, Leif Pierre, CCP, Henrik Scherstén, MD, PhD, Martin Silverborn, MD, PhD, Trygve Sjöberg, PhD, Ulla Westfeldt, MD, PhD, and Stig Steen, MD, PhD


First Human Transplantation of a Nonacceptable Donor Lung After Reconditioning Ex Vivo
Stig Steen, MD, PhD, Richard Ingemansson, MD, PhD, Leif Eriksson, MD, PhD, Leif Pierre, CPP, Lars Algotsson, MD, PhD, Per Wierup, MD, PhD, Qiuming Liao, MD, Atli Eyjolfsson, MD, Ronny Gustafsson, MD, PhD, and Trygve Sjöberg, PhD

Ex-vivo evaluation of donor lungs

History

Technique for Prolonged Normothermic Ex Vivo Lung Perfusion

Marcelo Cypel, MD, Jonathan C. Yeung, MD, Shin Hirayama, MD, Matthew Rubacha, MD, Stefan Fischer, MD, Masaki Anraku, MD, Masaaki Sato, MD, Stephen Harwood, MD, Andrew Pierre, MD, Thomas K. Waddell, MD, Marc de Perrot, MD, Mingyao Liu, MD, and Shaf Keshavjee, MD

J Heart Lung Transplant 2008;27:1319-25
Ex Vivo Evaluation

- Visual
- Physiological
- Biological
Gas for deoxygenation:
86% N$_2$, 8% CO$_2$, 6% O$_2$
Perfusion Solution

- Steen solution ®
- Heparin 10,000 IU/L
- Broad Spectrum ABX
- Methylprednisolone 500 mg
Graft Parameters

- **Pulmonary Vascular Resistance**
  \[ \text{PVR} = \frac{(\text{PAP} - \text{LAP}) \times 80}{\text{flow}} \text{ (Dynes x sec x cm}^{-5} \text{)} \]

- **Pulmonary Flow**
  \[ \text{PAF (L/min)} \]

- **Airway Pressures**
  - mean \( \text{AwP} \) and peak \( \text{AwP} \) (cm H\(_2\)O)

- **Oxygenation**
  \[ \text{PO}_2/\text{FiO}_2 \text{ (mm Hg) or } \Delta \text{ pv-paPO}_2 \]
Controlled Reperfusion

- PA pressure slowly increased to 15 mm Hg
- Temperature slowly increased to 37.5°C

to limit endothelial injury from hydrostatic pressure
Controlled Ventilation

- $V_T$ (6-8ml/kg) and $f$ (10 breaths/min) slowly increased
- PEEP of 5 cm H$_2$O
- FiO$_2$ = 21%
- Ventilation not started until lung temperature $= 32^\circ$ C

to limit alveolar injury from mechanical shear stress
## EVLP Perfusion Strategy - First Hour

### Controlled Reperfusion

<table>
<thead>
<tr>
<th>Perfusion Time (Minutes)</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>60 Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Perfusion Temp. (°C)</strong></td>
<td>20</td>
<td>30</td>
<td>32-35</td>
<td>37</td>
<td>37</td>
<td>37</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td><strong>Flow (% Calculated Flow)</strong></td>
<td>10</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>50</td>
<td>80</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td><strong>Ventilation</strong></td>
<td>none</td>
<td>none</td>
<td>start</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gas Exchanger</strong></td>
<td>none</td>
<td>none</td>
<td>start</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Left Atrial Pressure (mmhg)</strong></td>
<td>3-5</td>
<td>3-5</td>
<td>3-5</td>
<td>3-5</td>
<td>3-5</td>
<td>3-5</td>
<td>3-5</td>
<td>3-5</td>
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</table>

### Controlled Ventilation

<table>
<thead>
<tr>
<th>Perfusion Time (Minutes)</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>60 Maintenance</th>
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<tr>
<td><strong>Perfusion Temp. (°C)</strong></td>
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<td>30</td>
<td>32-35</td>
<td>37</td>
<td>37</td>
<td>37</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td><strong>Flow (% Calculated Flow)</strong></td>
<td>10</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>50</td>
<td>80</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td><strong>Ventilation</strong></td>
<td>none</td>
<td>none</td>
<td>start</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gas Exchanger</strong></td>
<td>none</td>
<td>none</td>
<td>start</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Left Atrial Pressure (mmhg)</strong></td>
<td>3-5</td>
<td>3-5</td>
<td>3-5</td>
<td>3-5</td>
<td>3-5</td>
<td>3-5</td>
<td>3-5</td>
<td>3-5</td>
</tr>
</tbody>
</table>

*Cypel M et al J Heart Lung Transplant 2008;27:1319-25*
# Table 2. EVLP Maintenance Strategy—Settings

<table>
<thead>
<tr>
<th>Measure</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal volume</td>
<td>6–8 ml/kg</td>
</tr>
<tr>
<td>PEEP</td>
<td>5 cm H$_2$O</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>7 breaths/min</td>
</tr>
<tr>
<td>FiO$_2$</td>
<td>21%</td>
</tr>
<tr>
<td>Flow rate</td>
<td>40% of estimated cardiac output</td>
</tr>
<tr>
<td>LAP</td>
<td>3–5 mm Hg</td>
</tr>
<tr>
<td>PAP</td>
<td>10–15 mm Hg</td>
</tr>
<tr>
<td>Recruitments</td>
<td>To PawP of 25 cm H$_2$O</td>
</tr>
</tbody>
</table>
Ideal Response

PVR
(Dynes x sec x cm⁻⁵)
Mean AwP
(cm H$_2$O)
$\text{PO}_2/\text{FiO}_2$ (mm Hg)

Onset of reperfusion

+ SEM

- SEM

min.
Ex-Vivo lung Perfusion
Initial Colorado Laboratory Experience

- Surgery
- Anesthesia
- Perfusion
- Donor Alliance
- Vitrolife
### Initial Laboratory Experience

**N=7**

<table>
<thead>
<tr>
<th>Procurement</th>
<th>Hours of Perfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>11</td>
<td>12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PaO2 with FiO2 100% (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procurement</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
</tbody>
</table>
Histology at 1, 6, and 12 Hours of Perfusion

1 hour perfusion

6 hours perfusion

12 hours perfusion
EVLP – Radiographic Assessment

Normal

Edema vs PNA
EVLP – Radiographic Assessment
Contusion
Novel Lung Trial: Normothermic Ex Vivo Lung Perfusion (EVLP) As An Assessment Of Extended/Marginal Donor Lungs

- **Centers**
  - University of Maryland
  - University of Colorado
  - Brigham and Women’s Hospital
  - Columbia University Medical Center
  - Duke University
  - University of Pennsylvania
  - Indiana

- **Sponsor**
  - XVIVO Perfusion
Novel Lung Trial: Normothermic Ex Vivo Lung Perfusion (EVLP) As An Assessment Of Extended/Marginal Donor Lungs

**Primary Outcome Measures:**
- 30 Day Mortality

**Secondary Outcome Measures:**
- PGD Scores at 0, 24, and 72 hours
- Intensive Care Unit Stay
- Day 7 Ventilator/ECMO Status
- 12 Month Survival
## Primary graft dysfunction scoring

<table>
<thead>
<tr>
<th>Grade</th>
<th>PaO2/FiO2</th>
<th>Radiographic Infiltrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&gt;300</td>
<td>Absent</td>
</tr>
<tr>
<td>1</td>
<td>&gt;300</td>
<td>Present</td>
</tr>
<tr>
<td>2</td>
<td>200-300</td>
<td>Present</td>
</tr>
<tr>
<td>3</td>
<td>&lt;200</td>
<td>Present</td>
</tr>
</tbody>
</table>
Inclusion criteria for EVLP assessment

- Single or Bilateral Lung Transplantation

- Donor \( \text{PaO}_2 / \text{FiO}_2 \leq 300\text{mmHg} \) during decision making time to use lungs,

OR If \( \text{PaO}_2 / \text{FiO}_2 > 300\text{mmHg} \) but following donor risk factors:
  - Multiple blood transfusions
  - Pulmonary edema detected on CXR, bronchoscopy or palpation lungs
  - Donation after cardiac death donors
  - Investigator evaluation of donor lung as "unsuitable" for standard criteria for lung transplant. List reason for "unsuitable" determination
- Steen solution ®
- Heparin 10,000 IU/L
- Broad Spectrum Antibiotics
- Methylprednisolone 500 mg
Inclusion criteria for transplant suitability

- $\Delta \text{PaO}_2 > 350 \text{ mmHg at, 3h or 4h of ex vivo perfusion}$
- Stability or improvement of other lung function parameters during EVLP (PVR, Compliance, Airway Pressures)
- Surgeon clinically satisfied with lung evaluation.
Exclusion criteria for transplant suitability

- $\Delta \text{PaO}_2 < 350 \text{ mmHg at 2h, 3h and 4h ex vivo perfusion}$
- $> 10\%$ Functional deterioration of other lung function parameters (PVR, compliance, PawP)
- Clinical evaluation from surgeon not satisfactory
All lungs included in the NOVEL trial have been rejected by all potential centers prior to being accepted for EVLP and potential transplant.
## U.S. EVLP Experience

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total # EVLP Patients enrolled up to date</td>
<td>58</td>
</tr>
<tr>
<td>Total # Control Patients enrolled up to date</td>
<td>55</td>
</tr>
<tr>
<td>Total Number offered/EVLP run but not transplanted</td>
<td>48</td>
</tr>
<tr>
<td>Total Number offered but did not procure/run EVLP</td>
<td>19</td>
</tr>
</tbody>
</table>
EVLP Case Report
Donor Data

- 62yo male
- Blunt right chest trauma
- CXR and CT c/w contusion
- PaO$_2$ 311mmHg @ sea level
- ~ 1000 miles from transplant center

Contralateral lung clear and accepted by other transplant center-Right lung offered to all potential centers and declined
EVLP Case Report
EVLP Physiologic Assessment @ 3hrs

- Flow rate 2.5 L/min
- PAP 18mmHg
- PVR 784 dyn*s/cm
- Vt 370ml w PEEP 5cm H₂O
- PAwP 11 cm H₂O
- CDyn 64.2ml/cm H₂O
- PaO₂ 370mmHg
EVLP CO-01

Postoperative Assessment

- Immediate PGD 0
- 24, 48 & 72hr PGD N/A (on 3L O₂)
- Transferred to floor @ 48hrs
- POD 5 Afib/flutter – cardioverted
- DC home POD 8

Immediate SICU
PaO₂ 322mmHg
## Colorado Experience

**n=5**

<table>
<thead>
<tr>
<th>Donor Age/Sex</th>
<th>Mechanism of death</th>
<th>Type of Transplant</th>
<th>Reason for marginality</th>
<th>Donor PO2</th>
<th>LAS</th>
<th>Recipient Diagnosis</th>
<th>30 day mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 M</td>
<td>Blunt trauma</td>
<td>Right Single</td>
<td>Contusion</td>
<td>499</td>
<td>57.9</td>
<td>COPD</td>
<td>no</td>
</tr>
<tr>
<td>38 M</td>
<td>Hanging</td>
<td>Left Single</td>
<td>Low Po2/hanging</td>
<td>278</td>
<td>30.9</td>
<td>COPD</td>
<td>no</td>
</tr>
<tr>
<td>31 F</td>
<td>Blunt trauma</td>
<td>Left single</td>
<td>Contusion</td>
<td>386</td>
<td>43.5</td>
<td>COPD</td>
<td>no</td>
</tr>
<tr>
<td>20 F</td>
<td>hanging</td>
<td>bilateral</td>
<td>hanging</td>
<td>500</td>
<td>85.0</td>
<td>ILD</td>
<td>no</td>
</tr>
<tr>
<td>46 F</td>
<td>Blunt trauma</td>
<td>Right single</td>
<td>Low PO2</td>
<td>256</td>
<td>48.8</td>
<td>ILD</td>
<td>no</td>
</tr>
</tbody>
</table>
## Colorado Experience

**n=5**

<table>
<thead>
<tr>
<th>patient</th>
<th>PGD-0hrs</th>
<th>PGD-24hrs</th>
<th>PGD72hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>extubated</td>
<td>extubated</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1</td>
<td>extubated</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>extubated</td>
<td>extubated</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1</td>
<td>extubated</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>extubated</td>
<td>extubated</td>
</tr>
</tbody>
</table>
Donor lungs do not meet standard donor criteria for transplantation

Donor lungs meet EVLP inclusion criteria

- Lung procurement and transfer to transplant center
- Potential recipient is called in

EVLP for 3h
Learning Points

Failed Ex-vivo 4/13/2012

23 year old donor due to blunt head trauma
Lungs turned down due to signs of aspiration
Learning Points

- $\text{PO}_2 > 400$
Learning Points
Successful Ex-vivo 4/21/2012

28y/o donor secondary to asphyxiation by hanging
23 y/o asphyxiation via hanging
Learning Points
Ex Vivo Machine Perfusion

Future of Organ Preservation?

LUNG  KIDNEY  LIVER  HEART
Remaining Questions

- best solution: electrolytes - nutrients?
- hypothermic versus normothermic?
- whole blood/RBC versus acellular?
- pulsatile versus non-pulsatile flow
- oxygenated vs deoxygenated blood
- maximum duration?
Potential Applications of EVLP

- to predict graft function in DCD lungs
- to re-evaluate graft from HBD
- to resuscitate lungs of inferior quality
- to prolong organ preservation
- to condition lungs against BOS
Conclusion

- predicts graft outcome
- new applications on horizon
- increase organ availability
- improve outcome?