Maximizing Donor Lungs:
Push and Mend

Amy Pope-Harman, MD

Klassen Research Day
January 22, 2015
Goals

- Why do we care about donors?
- Bad things happen to donor lungs
- Donor criteria history
- Where we can push the envelope
- Resuscitation
Why we care

Bad things do happen to donor lungs

Donor Criteria History

What can we push?

What can we fix?
Why should we care about lung donors?

- The Numbers
- The People
- The Longevity
The Numbers

Donor Shortage:

As of January 16, 1659 patients are listed for lung transplants in the US.

In 2014, there were 2146 additions to the waitlist.

In 2014, there were only 1572 transplants from 7102 donors.
  Down from 2013 -- only 22% of donors are lung donors.

UNOS lists 180 deaths on the list in 2014—does not include those removed or Status 7 when they became too ill to transplant.

Unsustainable: requires ever-increasing LAS to obtain offers.
The People—“Patients”

Patient JG

51 yo man with an 8 year history of sarcoidosis
10 L at rest, 25 with activity
Moderate PH
Listed quickly -- LAS 55
Died within 5 weeks, no offers
The Longevity

Recipient and Organ

Primary Graft Dysfunction can affect long-term survival:

Whitson et al.  JHLT 2007
Lung Donors

Why we care

Bad things can happen to donor lungs

Donor Criteria History

What can we push?

What can we fix and how?
<table>
<thead>
<tr>
<th>Complication</th>
<th>% Donors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>84%</td>
</tr>
<tr>
<td>Anemia</td>
<td>68%</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>58%</td>
</tr>
<tr>
<td>Diabetes Insipidus</td>
<td>52%</td>
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<tr>
<td>Hypoxemia</td>
<td>25%</td>
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</tbody>
</table>
Brain Death Effects

Dynamic effects on pulmonary vasculature
Upregulation of cytokines and lymphokines
Widespread microvascular endothelial changes
Increased expression cell adhesion molecules
Increased expression of MHC antigens
Other Problems with donor lungs:

Aspiration
Infection
Trauma
ICU environment and vulnerabilities
Pulmonary emboli

(Particularly bad prognosis—nearly 5 fold increase in risk of severe PGD for donor)

*Oto JHLD 2008*
Why we care

Bad things happen to donor lungs

Donor Criteria History

What can we push?

What can we fix and how?
Historic Criteria

Age < 55 yr
ABO blood group compatibility
Clear chest radiograph
PaO₂ ≥ 300 mm Hg on FiO₂ 100%
positive end-expiratory pressure ≤ 5 cm H₂O
≤ 20 pack-year smoking history
Absence of chest trauma
No aspiration or sepsis
Gram stain free of bacteria, fungus, and WBCs

Weill, Chest 2002
We are missing out on potential lungs
Why we care

Bad things happen to donor lungs

Donor Criteria History

What can we push?

What can we fix and how?
Age

Baldwin 2013:

Examination of OPTN Database:

- 65 yo donors

-one year survival similar
  (in recipients without high LAS score or extremes of age)

Baldwin et al AJT 2013
Radiographs in potential donors

110 potential lung donors at UCSF (42 that eventually came to transplant)

Densities in 37% of lungs

Worsening or widespread densities associated with increased rejection episodes in recipients (timing and degree of rejections were not reported)

McCowin J Heart Lung Transplant 2005
PaO2 $\geq$ 300 mm Hg on FiO2 100%

Not all agree this large a margin is predictive.

Oxygenation is an important indicator of adequate lung function.

Trend is probably more important.
Smoking in Donors

UNOS Database evaluation:
Single lungs from donors with greater than 20 pack/years 2005-2011
498 Transplants
Similar survival, similar freedom from BOS
Mortality worse with active donor smoking
(HR 1.23)

Taghavi et al JHLT 2013
Chest Trauma

Not much literature to guide us
Assure no immediate threat to recipient
    (airway defects, air leaks)
Reversible in donor likely equals reversible in recipient
Aspiration

No literature
Reversible chemical injury
Oropharyngeal bacteria are generally treatable
Trend in radiographs and oxygenation may be helpful
Microbiology

Gram-negative bacteremia
Mycobacterial infections of chest
Invasive fungal diseases
*Hepatitis C
*Hepatitis B surface antigen-positivity
*HIV/AIDS
Creutzfeldt–Jakob disease
West Nile virus
Severe acute respiratory syndrome (SARS)
Garrity et al JHLT 2005
Adenovirus
Bridges et al JTCS 1998

Donor lungs may be used with caution upon evidence of:

Gram-positive bacteremia
Mycobacterial infections outside the chest
Fungal airway colonization
Hepatitis B core antibody
Herpesviruses (HHV 6–8, simplex, varicella)
Cytomegalovirus
Epstein–Barr virus (though high risk if donor + / recipient -)
Garrity et al 2005
Other Pushing

DCD Donors:
Lungs maintain post arrest
Proposed employment of Ex-Vivo technology
Even without ex-vivo resuscitation, outcomes are good:
Multi-center Australian Trial: 174 DCD donors versus 503 standard
-28% increase donors
-PGD III  5.2% (versus 20% Brain dead donor)
-PF Ratio 315
-5-year survival 90% (versus 61% for standard donors)

Levey et al AJT 2012
Other Pushing

Not ready for prime time:

Lobar Transplants:
Mitilian reports 50 cases done for patients with small thoracic volumes
ECMO 10 recipients
Vent time > 10 days average
5-y survival 46%

*Mitilian et al EJCTS 2014*

Xenotransplant

In vitro Lung Culture
<table>
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<th>why we care</th>
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Resuscitating Lungs in Vivo

Reasonable hemodynamic and fluid management

Vent:
Most patients can be managed with “conventional” vent settings

Recruitment maneuvers may be of help

APRV – Graft Survival

*Hanna et al Arch Surg 2011*
Resuscitating Donor Lungs: Ex Vivo Lung Perfusion (EVLP)

First performed in 2001—Allows lungs to be ventilated, perfused, and assessed post procurement.
EVLP Technologies

Transmedics OCS (Organ Care System)  XVIVO Perfusion System (XPS)
How can EVLP help?

Improve organ injury and recondition organs
Assess organ function over time
Modify or protect organs against future injury
Allow accelerated study of new transplant interventions
Increase logistical options for transplants
<table>
<thead>
<tr>
<th>Study</th>
<th>EVLP Tx N</th>
</tr>
</thead>
<tbody>
<tr>
<td>HELP</td>
<td>20</td>
</tr>
<tr>
<td>Expanded HELP</td>
<td>61+</td>
</tr>
<tr>
<td>NOVEL</td>
<td>31</td>
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<tr>
<td></td>
<td>As of 3/15/2014 = 58</td>
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Clinical Trials

Courtesy XVIVO Perfusion
NOVEL Trial

- Prospective, non-randomized, multicenter, controlled clinical trial
  - University of Maryland Medical Center
  - Brigham and Women’s Hospital
  - NY Presbyterian-Columbia University Hospital
  - University of Colorado Medical Center
  - Duke University Medical Center
  - University of Pennsylvania Medical Center
NOVEL Trial Study Design

Donor Lungs Allocated per UNOS Standard Allocation Process (LAS Score and Donor/Recip Factors)

Rejected for Standard Transplant
Median $PO_2=341$

Lung Blocks Placed on EVLP N=54

Deemed Non-Transplantable N=25

Deemed Transplantable N=29

Recipients N=31

Accepted for Standard Transplant
Median $PO_2=421$

Deemed Transplantable N=31

Recipients N=31*
Unacceptable Donor Definition

- **Group A:** \( \text{PaO}_2/\text{FiO}_2 \leq 300\text{mmHg} \)
  
  OR

- **Group B:** \( \text{PaO}_2/\text{FiO}_2 > 300\text{mmHg} \)
  
  - One or more factors makes them unacceptable for transplant
    
    - Multiple blood transfusions.
    - Pulmonary edema detected via CXR, bronchoscopy or palpation of lungs.
    - Donation after Circulatory Death (DCD).
    - Investigator evaluation of donor lung as “unsuitable” for standard criteria for lung transplant.
NOVEL Trial Overview

Pre-EVLP Assessment
EVLP with STEEN Solution™
Post-EVLP

1hr 2hr 3hr 4hr

Physiological Parameters Assessed

• **XPS™ Hemodynamic Monitor**
  • PVR (Pulmonary Vascular Resistance)
  • PAP (Pulmonary Artery Pressure)
  • LAP (Left Arterial Pressure)

• **XPS™ Hamilton ICU Ventilator**
  • Peak awP (Peak Airway Pressure)
  • Mean awP (Mean Airway Pressure)
  • pPlat (peak Plateau)
  • cDyn (Dynamic compliance)
  • cStat (Static compliance)
  • $V_T$ (Tidal Volume)

• **Blood Gas Machine**
  • PaO2 (Pulmonary Artery Oxygen)
  • PvO2 (Pulmonary Vein Oxygen)

Transplanted
Not Transplanted

Courtesy XVIVO Perfusion
## NOVEL Trial Primary End Point

<table>
<thead>
<tr>
<th>Group</th>
<th>EVLP Transplant</th>
<th>Control Transplant</th>
<th>ISHLT Registry Reference*</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 day patient survival</td>
<td>97% (30/31)</td>
<td>100% (31/31)</td>
<td>94%</td>
</tr>
<tr>
<td>90 day patient survival</td>
<td>97% (30/31)</td>
<td>100% (31/31)</td>
<td>88%</td>
</tr>
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Courtesy XVIVO Perfusion
Novel Trial 12-Month Survival

NOVEL 12-Month Survival

Survival

Control (N=31)
EVLP (N=31)
ISHLT

Day

0 90 180 270 365

100%
94%
P = 0.35
88%
83%

0% 20% 40% 60% 80%
The First 50 Clinical EVLP: Toronto Experience

**Graphs**

**Graph A**: Survival plot showing percent survival.
- **Controls** (n=253) vs. **EVLP** (n=50).
  - **Survival Rate**: Controls vs. EVLP.
  - **Statistical Significance**: p=0.69.

**Graph B**: Survival plot showing percent survival.
- **Controls** (n=253) vs. **EVLP BDD** (n=28) vs. **EVLP DCD** (n=22).
  - **Survival Rate**: Controls vs. EVLP BDD vs. EVLP DCD.
  - **Statistical Significance**: p=0.71.

Cypel M et al., JTCVS 2012 144(5):1200-7
EVLP: French Experience

- 31 EVLP Lungs
- 81 Standard

Sage E et al., EJCTS 2014 1-6
Decrease PGD Risk

- Italian Study
- 8 EVLP
- 28 Standard
- PGD @ 0 hrs and 72 hrs

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 36)</th>
<th>Group A (n = 28)</th>
<th>Group B (n = 8)</th>
<th>P</th>
<th>Overall (n = 36)</th>
<th>Group A (n = 28)</th>
<th>Group B (n = 8)</th>
<th>P</th>
</tr>
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<tr>
<td>PGD 0-1</td>
<td>36 ± 4.1% (13)</td>
<td>29 ± 10.5% (8)</td>
<td>63 ± 43.3% (5)</td>
<td>0.11</td>
<td>62 ± 20.1% (22)</td>
<td>54 ± 19.8% (15)</td>
<td>88 ± 60.6% (7)</td>
<td>0.10</td>
</tr>
<tr>
<td>PGD 2</td>
<td>17 ± 5.4% (6)</td>
<td>21 ± 7.6% (6)</td>
<td>0% (0)</td>
<td>0.19</td>
<td>19 ± 6.0% (7)</td>
<td>21 ± 7.6% (6)</td>
<td>12 ± 7.9% (1)</td>
<td>0.65</td>
</tr>
<tr>
<td>PGD 3</td>
<td>47 ± 15.2% (17)</td>
<td>50 ± 18.3% (14)</td>
<td>37 ± 25.3% (3)</td>
<td>0.57</td>
<td>19 ± 6.0% (7)</td>
<td>25 ± 9.1% (7)</td>
<td>0% (0)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Boffini ME et al., EJCTS 2014 1-5
EVLP is Safe

<table>
<thead>
<tr>
<th>Lung Tx Outcomes</th>
<th>ISHLT* Reference Data</th>
<th>SRTR** Reference Data</th>
<th>NOVEL EVLP Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 day survival</td>
<td>94%</td>
<td>96%</td>
<td>97%</td>
</tr>
<tr>
<td>1 year survival</td>
<td>81%</td>
<td>82%</td>
<td>84%</td>
</tr>
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</table>

* ISHLT: International Society of Heart and Lung Transplant Registry.
** SRTR: Scientific Registry of Transplant Recipients.
EVLP Could Increase Lung Utilization

• HELP trial = 20 EVLP lung transplants. Lung utilization rate increased from 25% to 36%

• NOVEL trial = 54 initially unacceptable donor lungs placed on EVLP
  – 29 lung donors meeting acceptability for transplant into 31 recipients
Donor Shortage

How to do better:

- Obtain all appropriate donors
- Donor management should maintain all organs
- Optimize lung placement
- Keep open mind regarding donor quality, donor types (DCD), and advancing intra-and ex-vivo lung resuscitative measures
- Careful cooperative practice
Remember…

Be a Buckeye for Life
SUPPORT ORGAN AND TISSUE DONATION

Thanks to our tireless team!

NP:
Jodi Knisley

RNs:
Staci Carter
Karen Nicholas

SW:
Shawn Spence

Scheduling and other Magic:
Tina Devoe

Surgeons:
Bryan Whitson
Peter Lee
Ahmet Kilic
Robert Higgins

Pulmonologists:
Don Hayes
Steve Kirkby

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