Ex Vivo Reconditioning of Non-Heart-Beating Donor Lungs in a Preclinical Porcine Model

Delayed Perfusion Results in Superior Lung Function

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Presenter Disclosure

The following relationships exist related to this presentation:

No Relationships to Disclose
Lung Transplantation

• Lifesaving treatment for end-stage pulmonary disease
• Limited by donor organ shortages
  – Renewed interested in non-heart-beating (NHB) donation
  – Maastricht Categories
    • Uncontrolled:  I – dead on arrival to hospital  
                    II – failed resuscitation
    • Controlled:  III – withdrawal of life support, awaiting arrest  
                    IV – cardiac arrest in brain dead donor
  – NHB donor post-transplant function difficult to predict
Ex Vivo Lung Perfusion (EVLP)

• Normothermic acellular perfusion

• Conceived as a means for lung assessment *ex vivo*

• Possible rehabilitation of marginal lungs

• Many unknowns
  – Ideal timing of initiation
  – Potential for pharmacologic treatment
Hypothesis

I. EVLP will allow successful transplantation of uncontrolled NHB donor lungs

II. Immediate EVLP optimal
   – Eliminates cold ischemic time
   – Rapid initiation of treatment
NHB Donor (Maastricht I) Hypoxic Arrest
60 min “no touch” WIT

Perfadex Flush
Standard Lung Harvest

CSP Cold Static Preservation

Storage in 4°C Perfadex 4 hours

I-EVLP Immediate EVLP

Normothermic 37 °C EVLP 4 hours

Recipient left lung transplant

Reperfusion: 3.5 hrs. double-lung 30 min isolated left lung

D-EVLP Delayed EVLP

Storage in 4°C Perfadex 4 hours

Normothermic 37°C EVLP 4 hours
Groups

NHB Donor (Maastricht I)
Hypoxic Arrest
60 min “no touch” warm ischemia

Perfadex Flush
Standard Lung Harvest

CSP
Cold Static Preservation

I-EVLP
Immediate EVLP
Normothermic 37 °C EVLP
4 hours

D-EVLP
Delayed EVLP
Storage in 4°C Perfadex
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↓

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↓

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Recipient left lung transplant

Reperfusion: 3.5 hrs. double-lung
30 min isolated left lung
EVLP

- Perfusion at 37°C with Steen solution
  - Heparin – 10,000 IU
  - Methylprednisolone – 500 mg
  - Cefazolin – 500 mg

- ATL-1223 – 3 ng/kg/min
  - Selective adenosine 2A-receptor agonist
  - Decreases ischemia-reperfusion injury in lung transplantation

* Cypel et al. J Heart Lung Transplant 2008
**LaPar et al. J Thorac Cardiovasc Surg 2011
Transplant Lung Assessment

• Physiology
  – Oxygenation – \( \text{PO}_2: \text{FiO}_2 \)
  – Mean airway pressure
  – Pulmonary artery (PA) pressure

• Bronchoalveolar lavage (BAL) cytokine analysis

• Lung Injury Score
  • Neutrophil infiltration
  • Alveolar edema
  • Interstitial infiltrate

\[ \text{Summed Composite Score} \]
Oxygenation Improved in D-EVLP

![Graph showing oxygenation levels during different stages of transplantation.](image-url)

- **Stage of Transplantation**
  - Pre-euthanasia
  - 1HR EVLP
  - 4HR EVLP
  - End Transplant

- **PO$_2$ : FIO$_2$ (mmHg)**
  - CSP
  - I-EVLP
  - D-EVLP

- Statistical significance:
  - * $P<0.05$ vs. CSP
  - # $P<0.05$ vs. all
Oxygenation Improved in D-EVLP

**Stage of Transplantation**

- Pre-euthansia
- 1HR EVLP
- 4HR EVLP
- End Transplant

**PO$_2$:FIO$_2$ (mmHg)**

- CSP
- I-EVLP
- D-EVLP

* $P<0.05$ vs. CSP

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Oxygenation Improved in D-EVLP

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Oxygenation Improved in D-EVLP

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# $P<0.05$ vs. all

**PO$_2$**•FIO$_2$ (mmHg)

**Stage of Transplantation**

- Pre-euthansia
- 1HR EVLP
- 4HR EVLP
- End Transplant

**Lines and Legends**

- CSP
- I-EVLP
- D-EVLP
PA and Mean Airway Pressure Improved in D-EVLP

Pulmonary Artery Pressure

- CSP
- I-EVLP
- D-EVLP

Mean Airway Pressure

- CSP
- I-EVLP
- D-EVLP

# P<0.05 vs. all
EVLNP Decreased Proinflammatory Cytokines

- IL-1β
- IL-8
- TNF-α

* P<0.05 vs. CSP
# P<0.05 vs. all
Gross and Histologic Appearance
Gross and Histologic Appearance

CSP

I-EVLP

D-EVLP
Gross and Histologic Appearance

CSP

I-EVLP

D-EVLP
Gross and Histologic Appearance

CSP

I-EVLP

D-EVLP
Lung Injury Score Lower in D-EVLP

- **PMN/HPF**: *P < 0.05 vs. CSP
- **Alveolar Edema**: *
- **Interstitial Infiltrate**: # P < 0.05 vs. all
- **Composite Score**: # P < 0.05 vs. all
Summary

• Hypothesis I correct
  – Successful transplant of uncontrolled NHB donor lungs

• Hypothesis II incorrect
  – D-EVLP decreased lung injury
    • Improved lung physiology
    • Decreased proinflammatory cytokines
    • Preserved lung histology
  – Combination of cold-storage and normothermic EVLP superior to either alone
Mechanism?

– Systemic hypothermia beneficial after cardiac arrest
  • Suppressed inflammatory response
  • Decreased free radical production
  • Inhibition of apoptosis

– In NHB donors
  • Hypothermia may arrest ongoing tissue injury/inflammation
  • Avoid perfusion of a hostile organ
Mechanism?

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Conclusion

• Uncontrolled (Maastricht I) NHB donor lungs can be rehabilitated for successful transplantation

• Delayed EVLP is an effective strategy for rehabilitation of NHB donor lungs

• EVLP lung function predicts post-transplant function

• This strategy could be easily implemented into current protocols, potentially solving the donor organ shortage
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