The GOLD Study

Goal of Open Lung Ventilation in Donors

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Disclosures

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- R01 HL126176
- HL 110969
- AI 106764
- HL 112747
- NIH/FDA P50 project
- U01 Blood 268201100051

Clinical Trials supported by NHLBI
- U01 HL 10871301
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GlaxoSmithKline - ED sepsis grant

Amgen – TIMP3 for ALI
The Clinical Problem

• The demand for donor lungs far exceeds the available supply

Why are so few lungs transplanted?

• Donor factors: age, smoking, asthma, trauma to the lung

• But most common: Hypoxemia and radiographic infiltrates

• Why?
The BOLD Trial

Beta-agonists for Oxygenation in Lung Donors

A Randomized Trial of the Effects of Nebulized Albuterol on Pulmonary Edema in Brain-Dead Organ Donors


American Journal of Transplantation 2013; XX: 1–8

Accompanying Editorial: Research and Innovation in the Deceased Donor.
D. A. Gerber, A. Glazier, and S. Feng, AJT 2014 in press
BOLD Study Hypothesis

Administration of an inhaled beta-adrenergic agonist (albuterol) will:
1. improve donor oxygenation (primary endpoint)
2. Improve lung compliance and CXR
3. improve donor lung utilization rates
4. Improve pulmonary edema as measured in resected lungs
5. Improve recipient outcomes
Enrollment

- 591 donors enrolled (2007-2011)
- 506 donors eligible for inclusion in final analysis

Reasons for Exclusion (n = 86)
- Consent not productive, n = 47
- No baseline ABG obtained, n = 30
- No doses of study drug received, n = 5
- Study data missing n = 4

Albuterol treatment did not alter the PaO₂/FiO₂ ratio

![Graph showing PaO₂/FiO₂ ratio for Placebo and Albuterol treatment](image)
Why was albuterol not effective?

1. Duration of treatment inadequate?
2. Not effective in setting of lung injury?
3. Harmful effects counterbalance any benefit?
4. Primary endpoint too noisy?
5. CTDN has such a high utilization rate that not much room for optimization?
6. Pulmonary edema not as much of a problem as anticipated?

Significance of the BOLD trial

1. Among the first large randomized clinical trials in organ donors
2. Shows feasibility of large scale clinical trials in this population
3. Developed important clinical trial infrastructure and experience at CTDN
**Atelectasis is Common in Organ Donors in BOLD**

<table>
<thead>
<tr>
<th></th>
<th>% with atelectasis on CXR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enrollment</strong></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>189/418 (45%)</td>
</tr>
<tr>
<td>Right</td>
<td>101/417 (24%)</td>
</tr>
<tr>
<td><strong>Procurement</strong></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>162/409 (40%)</td>
</tr>
<tr>
<td>Right</td>
<td>83/411 (20%)</td>
</tr>
</tbody>
</table>

**Bilateral atelectasis**

![Bilateral atelectasis image]
Atelectasis at enrollment is associated with significantly worse oxygenation

* P < 0.005 vs all other groups

Atelectasis at procurement is associated with significantly worse oxygenation

* P < 0.05 vs all other groups
Bilateral atelectasis at enrollment or procurement is associated with the lowest rates of lung utilization.

Distribution of PEEP in BOLD:

- Mean = 1.81
- Std. Dev. = 2.038
- N = 500
Effect of a Lung Protective Strategy for Organ Donors on Eligibility and Availability of Lungs for Transplantation
A Randomized Controlled Trial
Luciana Mascia et al. JAMA 2010 304:2620-2627

Multicenter European randomized controlled trial of 2 ventilatory strategies for 6 hours in 118 organ donors early in donation process

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>Protective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal Volume</td>
<td>10 – 12 ml/kg PBW</td>
<td>6 – 8 ml/kg PBW</td>
</tr>
<tr>
<td>PEEP</td>
<td>3-5 cm H2O</td>
<td>8-10 cm H2O</td>
</tr>
<tr>
<td>Suctioning</td>
<td>Open Circuit</td>
<td>Closed Circuit</td>
</tr>
<tr>
<td>Recruitment Maneuvers</td>
<td>None</td>
<td>After ventilator disconnect</td>
</tr>
<tr>
<td>Apnea Test</td>
<td>100% FiO2</td>
<td>CPAP on vent</td>
</tr>
</tbody>
</table>
Conclusions from JAMA study

- Protective ventilation prevented deterioration of lung function in donors who entered study with good lung function
- Relatively small, short term study—not directly applicable to US organ donor management

- Not clear which aspect of protocol was protective
  - Low tidal volume
  - Recruitment maneuvers/suctioning method
  - Apnea testing
  - Higher PEEP
GOLD Study: Objective

• To assess whether ventilation with an open lung protective ventilatory strategy will improve donor lung utilization rates and donor oxygenation compared to a conventional ventilatory strategy

Inclusion criteria

– Brain death
– Consent for research from family
– Completion of organ donation process (at least one organ procured)
– Donor age >= 13 years old
– Coroner release for lungs to be procured for research for Matthay lab
Exclusion criteria

- Donation after cardiac death planned
- PaO2/FiO2 ratio > 450 (to exclude donors who already have excellent lung function)
- PaO2/FiO2 ratio < 150 (to exclude donors with a very low likelihood of lung utilization)
- Consent not productive (failure to complete the organ donation process)
- BMI > 40

Lung donation by PaO2/FiO2 ratio
Study Design

- Multicenter randomized trial (all CTDN hospitals)
- **Primary endpoint:** Donor lung utilization
- **Secondary endpoints (donor)**
  - Lung utilization in likely donors
  - Change in donor oxygenation
  - Static compliance of the respiratory system
  - Atelectasis scoring of the chest radiograph
  - Plasma biomarkers of lung injury/inflammation
  - Severity of pulmonary edema in rejected lungs
  - Other organ utilization (safety endpoint)

- **Secondary endpoints (recipient)**
  - Primary graft dysfunction
  - 30-day mortality
  - 1-year mortality

Ventilator Protocol

<table>
<thead>
<tr>
<th>Conventional</th>
<th>Open Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 ml/kg PBW</td>
<td>8 ml/kg PBW</td>
</tr>
<tr>
<td>PEEP 5</td>
<td>Reduce TV if Pplat&gt;30</td>
</tr>
<tr>
<td>Recruitment maneuvers</td>
<td>Recruitment maneuvers</td>
</tr>
<tr>
<td>Tracheal suctioning-open or closed circuit</td>
<td>Closed circuit if available</td>
</tr>
</tbody>
</table>
Study Flow

* Study ABGs and Challenge ABGs will be done on standard vent settings with FiO2 1.0, PEEP 5 for at least 20 minutes

Projected Enrollment

- Plan to enroll 400 subjects, 200 per arm
- Block randomization with varying block sizes
- Power if lung utilization increases from 25% to 40% (targeting group with midrange P/F from 150 – 450)
- 400 subjects will have 90% power to detect this difference
DSMB and Safety Oversight

• An independent DSMB will oversee the trial
• 2 interim analyses for safety and efficacy:
  – After 134 donors enrolled
  – After 268 donors enrolled

• Early stopping rules are based on donor lung utilization. Study can be stopped for safety, efficacy or futility

Acknowledgments

NIH NHLBI: R01 funding for GOLD study - 2014

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