ECMO for Severe Hypoxemic Respiratory Failure: Pro-Con Debate

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Case Presentation

Setting: Community hospital, November 2009

- 29 year old woman with no past medical history
- Presents with cough, myalgias, SOB
- CXR: LLL infiltrate
- Treated with azithromycin, discharged home
- Returns to hospital feeling much worse
  - Now severely hypoxemic
  - 1.5 weeks have elapsed since initial symptoms
- Brief trial of NIV fails, and she is intubated
Case presentation continued

- CXR now: Diffuse bilateral infiltrates
- Nasal wash: Positive for H1N1 influenza
- Treatment with oseltamavir, vancomycin, piperacillin/tazobactam, and doxycycline
- Oxygenation progressively worsens
  - Ventilator settings: Low tidal volumes, FiO2 1.0, PEEP 20
  - PaO2 44
- iNO added; PaO2 briefly improves to 70, but with frequent desat to SaO2 70%
- Question for UCSF: Is she a good candidate for ECMO?
Pro: ECMO for Severe ARDS

- Overview of talk
  - Basics of ECMO
  - Data on ECMO for severe ARDS
    - Prior to H1N1 epidemic
    - H1N1-specific
  - Lack of appealing alternatives
    - High-frequency ventilation
    - Inhaled nitric oxide
    - Prone positioning
    - Pharmacologic agents
  - When to consider referral to an ECMO center
ECMO: Extra-corporeal membrane oxygenation

• Veno-venous circuit that relieves lungs from role in gas exchange by oxygenating blood via extracorporeal oxygenator and removing CO₂
  – Veno-arterial circuit (ECLS) can replace cardiac function as well; akin to cardiopulmonary bypass

• Requires large bore IV access (17-27 French), anticoagulation

• Available only in referral centers with particular expertise in management

• Frequently used in NICU for management of neonatal respiratory distress syndrome
ECMO: Initial Experience in ARDS

- Initial studies in ARDS showed high mortality rate
  - High tidal volume ventilation continued
  - Larger cannulae, higher-dose anticoagulation
  - Initiated ECMO late in course of ARDS
  - Primarily V-A ECMO
    - Higher risk
    - Now using more V-V ECMO
  - More recent studies: More favorable data
ECMO for ARDS Due to Severe H1N1 Influenza

- *JAMA* 2009
- Descriptive study from Australia of all patients treated with ECMO during epidemic
- 68 patients with suspected or confirmed H1N1 on ECMO
  - 30% of those ventilated for H1N1
- Median age 34 yrs
- Mean P:F ratio 56, lung injury score of 3.8
- 48 of 68 survived to ICU discharge
  - 14 died
  - Remainder still in ICU at time of publication
Chest Radiograph and Computed Tomogram of 2 Patients Successfully Treated With ECMO for Confirmed 2009 Influenza A(H1N1)

### Severity of ARDS Before Commencement of ECMO

**Table 2. Severity of ARDS Before Commencement of ECMO**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>2009 Influenza A(H1N1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Confirmed Infection</td>
</tr>
<tr>
<td></td>
<td>(n = 53)</td>
</tr>
<tr>
<td>Ventilation parameters, median (IQR)</td>
<td></td>
</tr>
<tr>
<td>Lowest PaO₂/FiO₂ ratio</td>
<td>55 (48-65)</td>
</tr>
<tr>
<td>Highest FiO₂</td>
<td>1.0 (1.0-1.0)</td>
</tr>
<tr>
<td>Highest PEEP, cm H₂O</td>
<td>18 (15-20)</td>
</tr>
<tr>
<td>Highest peak airway pressure, cm H₂O</td>
<td>36 (34-40)</td>
</tr>
<tr>
<td>Lowest pH</td>
<td>7.2 (7.1-7.3)</td>
</tr>
<tr>
<td>Highest PacO₂, mm Hg</td>
<td>69 (54-86)</td>
</tr>
<tr>
<td>Highest tidal volume, mL/kg</td>
<td>5.6 (4.8-6.6)</td>
</tr>
<tr>
<td>Quadrants of radiograph infiltrate, No.</td>
<td>4 (4-4)</td>
</tr>
<tr>
<td>Acute lung injury score</td>
<td>3.8 (3.3-4.0)</td>
</tr>
<tr>
<td>Pneumothorax pre-ECMO, No. (%).</td>
<td>9 (17)</td>
</tr>
<tr>
<td>Rescue ARDS therapies used, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Recruitment maneuver</td>
<td>30 (66)</td>
</tr>
<tr>
<td>Prone positioning</td>
<td>11 (22)</td>
</tr>
<tr>
<td>High-frequency oscillation</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>19 (38)</td>
</tr>
<tr>
<td>Prostacyclin</td>
<td>12 (23)</td>
</tr>
</tbody>
</table>

Abbreviations: ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; FiO₂, fraction of inspired oxygen; IQR, interquartile range; PEEP, positive end-expiratory pressure.

Data were missing in 4 cases for PaO₂/FiO₂ ratio, in 4 cases for PEEP, in 17 cases for lung compliance, and in 5 cases for quadrants of radiograph infiltrate.

Clinical Outcomes post-ECMO

• Of 32 patients that had survived to hospital discharge at time of publication:
  – 31 were ambulatory
  – Median pulse ox on room air = 97%

• 14 died
  – Causes of death: 4 died from hemorrhage, 6 died from intracranial hemorrhage

• Overall survival rate = 79%
  – Dramatic improvement since trials in early 1980s
  – Attributed to use of lower tidal volume ventilation, viral pneumonia (higher survival rate with ECMO), more experience with ECMO
ECMO: CESAR Trial

- *Lancet* 2009
- Conducted in UK; n=180 patients aged 18-65
- Severe ARDS:
  - Hypercapnic acidosis with pH<7.2, and/or
  - Lung injury score > 3

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO₂/FiO₂</td>
<td>≥300</td>
<td>225-299</td>
<td>175-224</td>
<td>100-174</td>
<td>&lt;100</td>
</tr>
<tr>
<td>CXR alveolar consolidation</td>
<td>none</td>
<td>1 quadrant</td>
<td>2 quadrants</td>
<td>3 quadrants</td>
<td>4 quadrants</td>
</tr>
<tr>
<td>PEEP</td>
<td>≤5</td>
<td>6-8</td>
<td>9-11</td>
<td>12-14</td>
<td>≥15</td>
</tr>
<tr>
<td>Compliance</td>
<td>≥80</td>
<td>60-79</td>
<td>40-59</td>
<td>20-39</td>
<td>≤19</td>
</tr>
</tbody>
</table>

- Exclusion:
  - High pressure (peak > 30 cm H2O) or high FiO2 (>0.80) ventilation for more than 7 days; contraindication to anticoagulation
- Randomized to usual care OR transfer to an ECLS providing tertiary care hospital
ECMO: CESAR trial

- **Primary endpoint:** Death or severe disability at 6 months after treatment
  - 63% disability-free survival in ECMO group vs. 47% in conventional group (p=0.03)

- **Criticisms**
  - Only 75% of patients transferred for ECMO actually received it
    - 16 of 90 improved before ECMO initiated; 5/90 died before ECMO could be started
  - Real-life, practical trial
  - Other aspects of care were not protocolized, e.g. low tidal volume ventilation
    - Practical trial, like protocols in critical care: Not always clear which part of protocol makes the difference
Long Term Outcomes From ECMO

- **Glenfield Hospital ECMO Follow-Up Study**
  - 40 ECMO survivors
  - 11 patients had FEV$_1$ < 80% predicted
  - 6/40 patients felt that their activity was limited by functional status

- **SF-36 scores among ECMO survivors**
  - Lower than healthy controls
  - Higher than survivors of ARDS, advanced heart failure, ESRD patients
  - 64% were employed full time

Sidebotham et al, J Cardiothor Vasc Anesth 2009
If not ECMO, what are the alternatives?
High Frequency Oscillatory Ventilation (HFOV)

• High mean airway pressure
  – Goal: Recruit atelectatic lung, improve oxygenation

• Oscillating piston at high frequency (180-900 x/minute)
  – Very small tidal volumes (1-2.5 ml/kg)

• May require heavy sedation +/- paralysis

• Can lead to hypotension from high intrathoracic pressures

• Contraindications:
  – Shock
  – Severe acidosis
  – Intracranial hemorrhage
HFOV: The Evidence

- Several small observational studies suggesting benefit
- Two larger RCTs
  - One showed trend towards improved mortality in HFOV group (37 vs 52%, p=0.10)
- Several trials have suggested particular benefit if applied early
- Ongoing multicenter RCT’s now
- Difficult to transition to HFOV once patient is on maximal ventilator settings
Figure 3. Mechanism of Action and Inaction of Inhaled Nitric Oxide.

Panel A shows normal ventilation-perfusion. Hypoxic pulmonary vasoconstriction (Panel B) minimizes ventilation-perfusion mismatching in the presence of abnormal ventilation. Inhaled vasodilators with a short half-life improve oxygenation by increasing blood flow to ventilated lung units (Panel C). If a vasodilator is administered intravenously (Panel D) or if diseases are associated with dysregulated pulmonary vascular tone, such as sepsis and acute lung injury (Panel E), hypoxic pulmonary vasoconstriction is counteracted, leading to worsening oxygenation. Long-term administration of inhaled nitric oxide, with the accumulation of nitric oxide or leakage between lung units associated with collateral ventilation, as may occur in chronic obstructive pulmonary disease (Panel F), may negate the beneficial effects of inhaled nitric oxide on oxygenation.
Effect of nitric oxide on PaO2/FiO2 ratio at 24 hours

<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients with data</th>
<th>Ratio of means (95% CI)</th>
<th>Weight (%)</th>
<th>Ratio of means (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>11 10</td>
<td>0.95 (0.64 to 1.42)</td>
<td>3.8</td>
<td>0.95 (0.64 to 1.42)</td>
</tr>
<tr>
<td>Schwebel</td>
<td>9 10</td>
<td>1.20 (0.94 to 1.54)</td>
<td>8.5</td>
<td>1.20 (0.94 to 1.54)</td>
</tr>
<tr>
<td>Dellinger</td>
<td>120 57</td>
<td>1.27 (1.14 to 1.41)</td>
<td>24.9</td>
<td>1.27 (1.14 to 1.41)</td>
</tr>
<tr>
<td>Michael</td>
<td>16 16</td>
<td>1.28 (1.01 to 1.62)</td>
<td>9.1</td>
<td>1.28 (1.01 to 1.62)</td>
</tr>
<tr>
<td>Troncy</td>
<td>15 15</td>
<td>1.14 (0.94 to 1.39)</td>
<td>12.4</td>
<td>1.14 (0.94 to 1.39)</td>
</tr>
<tr>
<td>Dobyns</td>
<td>49 50</td>
<td>0.94 (0.77 to 1.15)</td>
<td>11.9</td>
<td>0.94 (0.77 to 1.15)</td>
</tr>
<tr>
<td>Lundin</td>
<td>78 66</td>
<td>1.05 (0.93 to 1.19)</td>
<td>21.1</td>
<td>1.05 (0.93 to 1.19)</td>
</tr>
<tr>
<td>Mehta</td>
<td>8 6</td>
<td>1.20 (0.82 to 1.75)</td>
<td>4.2</td>
<td>1.20 (0.82 to 1.75)</td>
</tr>
<tr>
<td>Park</td>
<td>11 6</td>
<td>1.03 (0.70 to 1.51)</td>
<td>4.1</td>
<td>1.03 (0.70 to 1.51)</td>
</tr>
<tr>
<td>Total</td>
<td>312 236</td>
<td>1.13 (1.04 to 1.23)</td>
<td>100.0</td>
<td>1.13 (1.04 to 1.23)</td>
</tr>
</tbody>
</table>
# Effect of nitric oxide on mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Deaths/patients randomised</th>
<th>Risk ratio (95% CI)</th>
<th>Weight (%)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dellinger³³</td>
<td>35/120</td>
<td>0.98 (0.60 to 1.59)</td>
<td>11.2</td>
<td>1.00 (0.94 to 1.30)</td>
</tr>
<tr>
<td>Michael³⁴</td>
<td>11/20</td>
<td>1.22 (0.65 to 2.29)</td>
<td>6.8</td>
<td>1.00 (0.94 to 1.30)</td>
</tr>
<tr>
<td>Troncy³⁵</td>
<td>9/15</td>
<td>1.13 (0.60 to 2.11)</td>
<td>6.7</td>
<td>1.00 (0.94 to 1.30)</td>
</tr>
<tr>
<td>Lundin³⁷</td>
<td>41/93</td>
<td>1.10 (0.78 to 1.55)</td>
<td>22.5</td>
<td>1.00 (0.94 to 1.30)</td>
</tr>
<tr>
<td>Payen³⁸</td>
<td>48/98</td>
<td>1.12 (0.83 to 1.50)</td>
<td>30.3</td>
<td>1.00 (0.94 to 1.30)</td>
</tr>
<tr>
<td>Mehta³⁹</td>
<td>4/8</td>
<td>1.50 (0.40 to 5.65)</td>
<td>1.5</td>
<td>1.00 (0.94 to 1.30)</td>
</tr>
<tr>
<td>Gerlach⁴⁰</td>
<td>3/20</td>
<td>0.75 (0.19 to 2.93)</td>
<td>1.4</td>
<td>1.00 (0.94 to 1.30)</td>
</tr>
<tr>
<td>Park⁴¹</td>
<td>4/11</td>
<td>1.09 (0.28 to 4.32)</td>
<td>1.4</td>
<td>1.00 (0.94 to 1.30)</td>
</tr>
<tr>
<td>Taylor⁴²</td>
<td>44/192</td>
<td>1.13 (0.77 to 1.66)</td>
<td>18.2</td>
<td>1.00 (0.94 to 1.30)</td>
</tr>
</tbody>
</table>

**Total**           | **577**                      |                       | **100.0**  | 1.10 (0.94 to 1.30) |

*Adhikari, N. K J et al. BMJ 2007;334:779*
Effect of nitric oxide on renal dysfunction (defined as new renal replacement therapy or new raised creatinine concentration)

<table>
<thead>
<tr>
<th>Study</th>
<th>No with renal dysfunction/patients randomised</th>
<th>Risk ratio (95% CI)</th>
<th>Weight (%)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dellinger³</td>
<td>Nitric oxide: 20/120, Control: 7/57</td>
<td>1.36 (0.61 to 3.02)</td>
<td>13.8</td>
<td></td>
</tr>
<tr>
<td>Lundin⁷</td>
<td>Nitric oxide: 28/80, Control: 12/74</td>
<td>2.16 (1.19 to 3.92)</td>
<td>24.8</td>
<td></td>
</tr>
<tr>
<td>Payen⁸</td>
<td>Nitric oxide: 33/89, Control: 26/90</td>
<td>1.28 (0.84 to 1.96)</td>
<td>49.7</td>
<td></td>
</tr>
<tr>
<td>Taylor¹²</td>
<td>Nitric oxide: 12/192, Control: 8/193</td>
<td>1.51 (0.63 to 3.61)</td>
<td>11.7</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>Nitric oxide: 481, Control: 414</td>
<td>1.50 (1.11 to 2.02)</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

Prone positioning

• Better matching of ventilation and perfusion
• Opening of dependent collapsed lung segments
• Improves oxygenation in about 70% or patients
• May be challenging to implement clinically
  – Special beds available
  – Attention to pressure-related complications
  – Attention to tubes and lines during turning procedure
• Does it improve outcomes?
Figure 1. Kaplan–Meier Estimates of Survival at Six Months. The status at 183 days was known for all but seven patients (four in the prone group and three in the supine group). The difference between groups was not significant (P=0.65 by the log-rank test).

Gattinoni et al, NEJM 2001
French study of proning in acute hypoxemic respiratory failure


No. at Risk
Supine Position 378 314 273 257 244 234 226 220 219 218
Prone Position 413 346 302 279 258 246 242 237 234 234

Log-Rank $P = .34$
Prone positioning in pediatric ALI

Table 3. Primary and Secondary Outcome Variables*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Supine (n = 50)</th>
<th>Prone (n = 51)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of ventilator-free days from 1-28 d, mean (SD)</td>
<td>15.8 (8.5)</td>
<td>15.6 (8.6)</td>
<td>.91</td>
</tr>
<tr>
<td>Alive and ventilator-free on day 28, No. (%)</td>
<td>43 (86)</td>
<td>41 (80)</td>
<td>.45</td>
</tr>
<tr>
<td>Mortality, No. (%)</td>
<td>4 (8)</td>
<td>4 (8)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>No. of days to recovery of lung injury, median (IQR)‡</td>
<td>5 (3-9)</td>
<td>4 (2-9)</td>
<td>.78</td>
</tr>
<tr>
<td>No. of days without failure of circulatory, neurological,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>coagulation, hepatic, and renal organs from 1-28 d, median (IQR)§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worse score from PICU admission to hospital discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(or day 28), No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCPC</td>
<td>11 (22)</td>
<td>6 (12)</td>
<td>.16</td>
</tr>
<tr>
<td>POPC</td>
<td>14 (29)</td>
<td>8 (16)</td>
<td>.12</td>
</tr>
</tbody>
</table>

25 Years of Failed Drug Trials for ARDS

- Corticosteroids
- Surfactant
- Prostaglandin E1
- Anti-endotoxins
- Anti-cytokines
- Procysteine
- Nitric oxide
- Ibuprofen
- Ketoconazole
- Lisofylline
- Soluble neutrophil elastase inhibitor
- sPLA$_2$ inhibitor
- Activated Protein C
- Inhaled beta-agonists
When to Consider Referral for ECMO?

- No firm criteria
- Criteria from CESAR trial:
  - Lung injury score > 3, or
  - Hypercapnic respiratory failure with pH<7.2
- Other key criteria:
  - Respiratory failure judged to be reversible
  - Early in course of disease
  - No contra-indication to anticoagulation
- Considering other “rescue” therapies
Summary: Support for ECMO for Severe ARDS

- Timely recent data supporting its use in specific settings:
  - Referral to ECMO-providing center for severe ARDS
  - Severe H1N1 pneumonia leading to ARDS

- Lack of viable alternatives with demonstrated mortality benefit
Case Presentation: Follow-Up
Case Presentation – Follow-Up

- Patient was transferred from outside hospital to UCSF with critical care MD in ambulance
- Went straight to OR for veno-venous cannulation (dual lumen)
  - PaO2 went from 48 to 71 in OR
  - SaO2 from 80% to 96% in 2 minutes on circuit
- Weaned off iNO
- Decannulated after 10 days on ECMO circuit
- On trach collar 3 days later
- Transferred back to referring facility off ventilator, intact mental status, hemodynamically stable