REFRACTORY HYPOXEMIA

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Joseph Levitt, MD, MSc, received his medical degree from the University of Minnesota. He did his resident training in Internal Medicine at the University of Chicago and fellowship training in Pulmonary and Critical Care Medicine at the University of Chicago and Stanford University. Dr. Levitt received an NIH Career Development Award to study the treatment of early Acute Lung Injury prior to onset of respiratory failure. He has been the site-Principal Investigator at Stanford for the ARDS Network and is the current site-PI for the NHLBI Network for the Prevention of Acute Lung Injury (PETAL). Dr. Levitt serves as an Assistant Professor of Medicine at Stanford University and the Program Director for the Pulmonary and Critical Care Medicine Fellowship.
REFRACTORY HYPOXEMIA: What is it and what can we do about it?

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CALIFORNIA THORACIC SOCIETY
JANUARY 18-19, 2019

CONFLICT OF INTEREST

NONE
REFRACTORY HYPOXEMIA: WHAT IS IT?

Original ARDSNet Low Tidal Volume Trial
• Targeted SpO₂ 88 – 95% or PaO₂ 55 – 80 mmHg
• Treatment arm had lower PaO₂ but better survival

So it’s not that!

REFRACTORY HYPOXEMIA: WHAT IS IT?

Recent EOLIA (ECMO) Trial
• Allowed crossover for SpO₂ < 80% for 6 hours
• 57% 60-day mortality despite receiving ECMO

Can we agree that it is that?
Shunt – Room Air

O₂ content = 
\[1.34 \times Hgb \times Sat\% + 0.003PaO₂\]

Shunt – 100% FiO₂

PaO₂ = 40
Sat = 75%
PACO₂ = 45

PaO₂ = 57
Sat = 87.5%

PaO₂ = 100
Sat = 100%
PaCO₂ = 40

PaO₂ = 40
Sat = 75%
PACO₂ = 45

PaO₂ = 57
Sat = 88%

PaO₂ = 500
Sat = 100%
PaCO₂ = 40

PaO₂ = 270
Sat = 100%
PaCO₂ = 40
Shunt – 100% FiO₂ & Shock

- pAO₂ = 500
- pACO₂ = 40

PaO₂ = 27
Sat = 50%
PACO₂ = 45

PaO₂ = 40
Sat = 75%

PaO₂ = 500
Sat = 100%
PaCO₂ = 40

INTRACARDIAC SHUNT

- Submassive Pulmonary Embolism with R to L shunt through patent PFO (up to 30% of population)
- Consider TPA for refractory hypoxemia
Multicenter clinical trials that Improved Oxygenation but Failed to improve Mortality

- 310 patients with acute hypoxic respiratory failure
  - RR > 25; P/F ratio < 300 on ≥ 10 L/min O₂
  - And PCO₂ ≤ 45 mmHg
- Randomized 1:1:1 to:
  - Continue standard O₂ vs. HFNC O₂ vs. Noninvasive ventilation
- Primary endpoint: Rate of intubation at 28 days
HIGH-FLOW OXYGEN

- Trend toward reduced intubations
- Significant reduction in intubation rate if P/F < 200...
- But, post-hoc analysis

![Graph](image1)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Group</th>
<th>P Value</th>
<th>Odds Ratio or Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death in ICU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted analysis</td>
<td>0.047</td>
<td>1.85 (0.84-4.09)</td>
<td>2.55 (1.21-5.35)</td>
</tr>
<tr>
<td>No. of patients</td>
<td>12</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>% of patients (95% CI)</td>
<td>11 (6-19)</td>
<td>19 (12-28)</td>
<td>25 (17-33)</td>
</tr>
<tr>
<td>Adjusted analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.36 (1.18-4.70)</td>
<td>2.33 (1.22-4.47)</td>
<td>2.36 (1.18-4.70)</td>
</tr>
<tr>
<td>% of patients (95% CI)</td>
<td>12 (7-20)</td>
<td>23 (16-31)</td>
<td>28 (21-37)</td>
</tr>
<tr>
<td>Adjusted analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
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</tr>
</tbody>
</table>

Table 2. (Continued.)
HIGH-FLOW NASAL CANNULA OXYGEN

• More comfortable and better tolerated
• Allows ongoing enteral nutrition and communication
• Likely reduces need for invasive mechanical ventilation and may increase survival
  • Likely reduces dead space +/- benefit of minimal PEEP
• Should probably be 1st treatment for refractory hypoxemia

• Noninvasive ventilation should be reserved for hypercapnic respiratory failure or CHF

PULMONARY VASCULAR VASODILATORS

• Inhaled Nitric Oxide and Prostacyclin (Epoprostenol) consistently shown to:
  • Reduce pulmonary vascular resistance
  • Transiently improve oxygenation
• But, no survival benefit or shorter time to extubation
  • Generally not recommended for treatment of ARDS
• But, Epoprostenol much cheaper than iNO and may have benefit in select cases
  • < 20% Mortality from ARDS due to refractory hypoxemia*

*Stapleton et al, Chest 2005
HIGH PEEP
• 3 large RCT’s demonstrated improved oxygenation with High vs. Standard PEEP†*#
• Increased P/F ratio and lung compliance
• But, at higher plateau and mean airway pressures
• No overall mortality benefit
• Phase II RCT Esophageal balloon guided transpulmonary PEEP vs. Standard PEEP (Talmor, NEJM 2009)
•Stopped early for meeting primary endpoint of improved oxygenation
• JAMA meta‐analysis (Brielet al, 2010)
  • Survival benefit with moderate‐severe ARDS (P/F < 200)
  • ARDSNet, NEJM 2004
  • Meade, JAMA 2008
  • EXPRESS, JAMA 2008

PATIENT-VENTILATOR DYSSYNCHRONY WITH LUNG-PROTECTIVE VENTILATION

Double-stacking
Large tidal volume
Loss of PEEP
NEUROMUSCULAR BLOCKADE (PARALYSIS)

• 340 patient RCT ARDS (P/F < 150) Paralysis vs. Heavy Sedation (Ramsay Score 6 both arms)
  • Overall mortality benefit (primarily with P/F < 120)
  • Higher P/F at 7 days but not 24 and 72 hours
• Re-Evaluation of Systemic Early Neuromuscular Blockade (ROSE)
  • 1400 patient PETAL Network trial
  • Stopped early at 1000 patients (results pending)

BASELINE IN SUPINE POSITION

AFTER 12 HOURS IN PRONE POSITION
PRONE POSITIONING

• 2 large RCT’s (Guerin, JAMA 2004; Taccone JAMA 2009)
  • Improved oxygenation
  • No mortality benefit
• Meta-analysis 1867 patients (Gattinoni AJRCCM 2010)
  • Lower mortality in patients with P/F < 100
• Most recent RCT (Guerin NEJM, 2013)
  • 466 pts w/ severe ARDS (P/F < 150 on FiO₂ > 0.6)
  • Reduced mortality (16% vs. 33%, P<0.001)
  • No increased complications from proning
  • ARDSNet Low PEEP protocol for both groups

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO)

• 249 patients with:
  • P/F < 50 for > 3 hours or < 80 for > 6 hours OR
  • pH < 7.25 and PCO₂ > 60 mmHg AND
  • FiO₂ ≥ 80% and PEEP ≥ 10 mmHg
  • Proning and paralysis encouraged before enrollment
• Randomized to ECMO or Express trial (High PEEP) protocol
• Cross-over allowed if SpO₂ < 80 for 6 hours and no irreversible multiorgan failure
EOLIA TRIAL

- Stopped early for futility (249 of 331 pts)
- 60-day Mortality 35% vs 46% (p = 0.09)

Table 1. End Points.1,2

<table>
<thead>
<tr>
<th>End Point</th>
<th>ECMO Group (N=249)</th>
<th>Control Group (N=182)</th>
<th>Risk Ratio w/ Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point: mortality at 60 days — no. (%)</td>
<td>44 (55)</td>
<td>57 (44)</td>
<td>0.76 (0.53 to 1.04)</td>
<td>0.09</td>
</tr>
<tr>
<td>Key secondary and patient treatment failure at 60 days — no. (%)</td>
<td>61 (28)</td>
<td>70 (34)</td>
<td>0.62 (0.41 to 0.92)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Other end points:
- Mortality at 90 days — no. (%) | 63 (26) | 55 (25) | 0.88 (0.62 to 1.23) |
- Median length of stay (interquartile range) — days
  - In the ICU | 25 (23–34) | 18 (9–29) | 5 (3–10) |
  - In the hospital | 36 (28–48) | 28 (21–39) | 8 (6–22) |
- Median days free from mechanical ventilation (interquartile range) | 23 (0–49) | 9 (3–34) | 20 (3–12) |
- Median days free from vasopressor use (interquartile range) | 49 (0–146) | 40 (0–133) | 9 (6–51) |
- Median days free from renal replacement therapy (interquartile range) | 10 (0–40) | 12 (3–57) | 18 (9–51) |
- Pneumonia — no. (%) | 82 (35) | 111 (55) | 0.74 (0.54 to 1.01) |
- Recruitment events — no. (%) | 27 (03) | 54 (29) | 0.5 (0.32 to 0.80) |
- Inhaled nitric oxide or prostacyclin — no. (%) | 75 (58) | 104 (55) | 0.73 (0.53 to 1.00) |
- Glucose control — no. (%) | 83 (51) | 87 (48) | 0.92 (0.70 to 1.20) |

Figure 2. Kaplan–Meier Survival Estimation during the First 60 Days of the Trial.

DIURESIS

ARDSNet FACCT (NEJM 2006)

- Conservative vs. Liberal fluid strategy
- Improvement in Oxygenation Index but not P/F ratio (higher PEEP in Liberal fluid arm)
- Shorter duration of mechanical ventilation
CONCLUSIONS

• Important to distinguish **clinically-relevant refractory hypoxemia**
  • Consider intracardiac shunt
• High-Flow Nasal Cannula Oxygen should be 1st line
  • Noninvasive ventilation reserved for hypercapnia or CHF
• 3 P’s of LPV
  • PEEP, proning, and paralysis
• ECMO improves survival
  • Likely 10 – 30% absolute risk reduction in select patients
PRE-TEST QUESTION 1

A 50 y.o. previously healthy female is admitted to the ICU for pneumonia and sepsis. She is intubated for hypoxemic respiratory failure after failing a trial of HFNC O₂. Post-intubation CXR shows bilateral infiltrates. Current ventilator settings are AC with a 6 cc/kg TV PBW, RR of 30, PEEP 10 cmH₂O, FiO₂ 0.70 with a plateau pressure (Ppl) of 29 cmH₂O. Current SpO₂ is 90% with an ABG of 7.36/PaO₂ 60/PaCO₂ 45/HCO₃⁻ 24. Evidence-based treatment strategies include:

A. Initiate neuromuscular blockade with cisatricurium
B. Initiate prone positioning for 16 hours per day
C. Increase PEEP to 20 cmH₂O and decrease TV to 4 cc/Kg PBW as necessary to keep Ppl < 35 cmH₂O
D. Continue current ventilator settings without change
E. B,C, and D
F. All of the above

PRE-TEST QUESTION 2

2 days later the same patient is now paralyzed on AC with RR 35, TV 4 cc/kg, PEEP 22, FiO₂ 1.0, Ppl of 32 cmH₂O with an ABG of pH 7.25/PaO₂ 54/PaCO₂ 52/HCO₃⁻ 20. Her MAP is 65 mmHg on norepinephrine 10 mg/min and vasopressin 0.04 u/hr. Her CVP is 8 mmHg with a ScVO₂ of 72% without signs of volume overload. Her serum Cr has doubled to 2.5 mg/dL in 48 hours, but she has no other evidence of irreversible organ failure. Evidence-based treatment strategies include:

A. Start inhaled Epoprostenol at 20 ng/kg/min
B. Start diuresis with iv furosemide to achieve a CVP of ≤ 4 mmHg
C. Initiate prone positioning for 16 hours/day with consideration for starting ECMO if not improved in 24 hours
D. Repeat ABG in 6 hours and initiate cannulation for venovenous ECMO if PaO₂ still < 80 mmHg
E. C and D
POST-TEST QUESTION 1

A 50 y.o. previously healthy female is admitted to the ICU for pneumonia and sepsis. She is intubated for hypoxemic respiratory failure after failing a trial of HFNC O₂. Post-intubation CXR shows bilateral infiltrates. She appears comfortable on ventilator settings of AC with a 6 cc/kg TV PBW, RR of 30, PEEP 10 cmH₂O, FiO₂ 0.70 with a plateau pressure (Ppl) of 29 cmH₂O. Current SpO₂ is 90% with an ABG of 7.36/PaO₂ 60/PaCO₂ 45/HCO₃⁻ 24. Evidence-based treatment strategies include:

A. Initiate neuromuscular blockade with cisatricurium for 48 hours
B. Initiate prone positioning for 16 hours per day
C. Increase PEEP to 20 cmH₂O and decrease TV to 4 cc/Kg PBW as necessary to keep Ppl < 35 cmH₂O
D. Continue current ventilator settings without change
E. B, C, and D
F. All of the above

ANSWER 1

The patient is currently meeting target SpO₂ of 88-95% or PaO₂ of 55-80 mmHg on ARDSNet LPV settings with standard PEEP. Changes to ventilator settings with sole goal of improving oxygenation are unnecessary and could be harmful. While no RCT has shown high PEEP to be improve survival relative to current settings, a meta-analysis of 3 large trials suggested benefit of high PEEP for patients with a P/F ratio < 200. Additionally, RCT’s have suggested benefit for 48 hours of neuromuscular blockade with cisatricurium as well as for prone positioning for patients with a P/F < 150 on 10 cmH₂O of PEEP. However, some equipoise remains regarding benefit of these additional therapies in patients adequately treated with standard LPV. Therefore, F (All of the above) is the best answer.
PRE-TEST QUESTION 2

2 days later the same patient is now paralyzed on AC with RR 35, TV 4 cc/kg, PEEP 22, FiO₂ 1.0, Pp of 32 cmH₂O with an ABG of pH 7.25/PaO₂ 54/PaCO₂ 52/HCO₃⁻ 20. Her MAP is 65 mmHg on Norepinephrine 10 mg/min and vasopressin 0.04 u/hr. Her CVP is 8 mmHg with a ScVO₂ of 72% without signs of volume overload. Her serum Cr has doubled to 2.5 mg/dL in 48 hours, but she has no other evidence of irreversible organ failure. Evidence-based treatment strategies include:

A. Start inhaled Epoprostenol at 20 ng/kg/min
B. Start diuresis with iv furosemide to achieve a CVP of ≤ 4 cmH₂O
C. Initiate prone positioning for 16 hours/day with consideration for starting ECMO if not improved in 24 hours
D. Repeat ABG in 6 hours and initiate cannulation for venovenous ECMO if PaO₂ still < 80 mmHg
E. C and D

ANSWER 2

Despite management with standard ARDSNet LPV, the patient’s condition has progressed and she has been appropriately paralyzed and placed on High PEEP. However, she is not currently meeting her oxygenation target (PaO₂ 55-80) and now has clinically relevant refractory hypoxemia. Starting inhaled Epoprostenol would likely lead to a transient improvement in oxygenation, however she does not appear to have a rapidly reversible cause of her hypoxemia and Epoprostenol is unlikely to change her overall outcome (A is incorrect). While the ARDSNet FACTT trial supports a conservative fluid strategy targeting a CVP ≤ 4 mmHg, the protocol only applied after resolution of shock. The patient currently has an intermediate level CVP on vasopressors with a rising Cr. Diuresis would not likely be helpful unless evidence of significant volume overload is present (B is incorrect). The patient currently meets criteria for a trial of prone positioning, especially if not currently at a center with expertise in ECMO. However, she is failing current standard therapy and is otherwise healthy without irreversible organ damage and would likely benefit from venovenous ECMO if she has a P/F ratio persistently < 80 for 6 hours per the recent EOLIA trial inclusion criteria. Therefore, E (C and D) is the best answer.