ADVANCES IN VENTILATOR MANAGEMENT OF ARDS

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Assistant Professor of Medicine

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Angela Rogers, MD, MPH, received her medical degree from Harvard Medical School, and her Masters in public health from the Harvard School of Public Health, and pursued post-graduate training at the Brigham and Women’s Hospital and Harvard Combined fellowship. She is an Assistant Professor in Pulmonary and Critical Care Medicine at Stanford University, where her research focuses on using genetics and genomics to identify novel biology in ARDS.
Advances in Mechanical Ventilator Management in ARDS

Angela Rogers
Stanford University
California Thoracic Society
January 18, 2019

Conflict of Interest

• I have no conflicts of interest
Learning Objectives

Mechanical Ventilation in ARDS:
• High flow oxygen therapy in early hypoxemic respiratory failure
• The critical importance of low tidal volume/low pressure ventilation
• PEEP in ARDS: Is there a role for personalized titration?
• New data for the role of ECMO in severe ARDS

A classic case of ARDS

• Intubated
• Acute
• P:F ratio <300
• Bilateral opacities
• Not explained by edema
Definition of ARDS

Acute Respiratory Distress Syndrome
The Berlin Definition
The ARDS Definition Task Force

• Bilateral infiltrates, acute (<7 days), not entirely explained by CHF, on 5 of PEEP
• Analyzed data from 7 ARDS datasets and >4400 patients
  • Severity classification:
    • Mild: PaO₂:FIO₂ 200 - ≤300
    • Moderate: PaO₂:FIO₂ 100 - ≤200
    • Severe: PaO₂:FIO₂ ≤100
  • Associated with mortality
    • 27%, 32%, and 45% with increasing severity

JAMA. 2012,307, 2526-2533

What if it’s not quite ARDS?

What about this patient?:
• Not intubated!
• PO2 72 on 100% NRB
• Bilateral opacities
Hypoxic Respiratory Failure (HRF) definition in FLORALI High Flow O₂ Trial

High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure

- Respiratory rate > 25
- PaO₂:FIO₂ < 300 on at least 10L/min flow x 15 min
- PaCO₂ <45
- No chronic respiratory failure

**NEJM. 2015,372, 2185-2196**

Treatment of Early HRF

- Primary outcome: intubation rate
- Secondary outcomes:
  - ICU & 90-day mortality
  - Vent-free days by day 28

**NEJM. 2015,372, 2185-2196**
High flow for early HRF

Entire Cohort

Days since enrollment

Incidence of intubation

NIPPV

Standard O₂

High Flow O₂

P=0.17 by log-rank test

NEJM. 2015,372, 2185-2196

High flow for early HRF

Patients with P:F ≤ 200

Days since enrollment

Incidence of intubation

NIPPV

Standard O₂

High Flow O₂

P=0.009 by log-rank test

NEJM. 2015,372, 2185-2196
High flow for early HRF

**Take home #1:**

- Prior to intubation in acute hypoxemic respiratory failure, consider high flow oxygen
  - Reduced mortality
  - Decreases need for intubation in sickest patients ($\text{PaO}_2:\text{FiO}_2 \leq 200$).
What if it is ARDS?

What is the #1 thing we can do for this patient?

The #1 Way to treat ARDS: Low tidal volume ventilation

- Multicenter RCT
- 861 patients with ARDS (P:F ≤ 300)
- Randomized to 6-8 vs. 10-12 ml/kg TV
- Target plateau pressure < 30

<table>
<thead>
<tr>
<th></th>
<th>Low Tidal Volume</th>
<th>Traditional Tidal Volume</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death before discharge</td>
<td>31.0</td>
<td>39.8</td>
<td>.007</td>
</tr>
<tr>
<td>Ventilator free days</td>
<td>12</td>
<td>10</td>
<td>.007</td>
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<tr>
<td>Organ-failure free days</td>
<td>15</td>
<td>12</td>
<td>.006</td>
</tr>
</tbody>
</table>

*NEJM*. 2000,342, 1301-1308
What helps mortality in ARDS?

Definitive

Low tidal volume ventilation

How good are we at implementing low tidal volume ventilation?: Lung Safe study in JAMA, 2016

- 459 ICUs from 50 countries across 5 continents x 1 month
- 29144 admitted
  - 10% fulfilled ARDS criteria
  - 23% of patients requiring mechanical ventilation

*JAMA.* 2016,315, 788-800
How good are we at implementing low tidal volume ventilation?: Lung Safe study in JAMA, 2016

- High mortality for ARDS in Lung Safe:
  - 34% mild
  - 40% moderate
  - 46% severe

- Ventilator strategy not ideal:
  - 1/3 of patients never recognized to have ARDS
  - $P_{plat}$ measured in 40%
  - <2/3 receive TV $\leq 8$ mg/kg

- Contrast with clinical trial mortality: 2000-2011

How good are we at implementing low tidal volume ventilation?: Lung Safe study in JAMA, 2016

Ventilator strategy in LUNG SAFE:
- 1/3 of patients never recognized to have ARDS
- $P_{plat}$ measured in 40%
- Less than 2/3 received TV $\leq 8$ mg/kg
ARDS is not unusual

Take home #2:

- ARDS is not unusual
- In real world practice:
  - mortality remains high
  - implementation of low tidal volume low pressure ventilator strategy is far from 100%
What helps beyond low tidal volume?

2 strategies for more severe ARDS
(P:F<150)

Neuromuscular blockade in ARDS

- Multicenter RCT
- 340 patients with early, moderate-severe ARDS (P:F<150)
- Randomized to 48hr cis-atracurium vs placebo
- All received standard low tidal volume ventilation

*NEJM. 2010, 373: 1107-16*
Paralysis in severe ARDS

Lower hazard for death (.68, p=.04)
31.6% vs 40.7% 90-day mortality (p=.08)

NEJM. 2010, 373: 1107-16

Does treatment improve ARDS mortality?

Definitive
- Lung protective ventilation

Probably*
- Neuromuscular blockade (P:F<150)

* Probably = at least one multicenter RCT supports
Prone positioning in severe ARDS

Prone Positioning in Severe Acute Respiratory Distress Syndrome

- Multicenter RCT
- 466 patients with early, moderate-severe ARDS (P:F<150)
- Randomized to 16h/day prone positioning vs standard low tidal volume ventilation

*NEJM*. 2013, 368: 2159-67

Probable of survival

Prone vs Supine

16% vs 32.8% 28d mortality (p<.001)
23.6 vs 41% 90d mortality (p<.001)

*NEJM*. 2013, 368: 2159-67
Does treatment improve ARDS mortality?

Definitive

- Lung protective ventilation

Probably*

- Neuromuscular blockade (P:F<150)
- Prone positioning (P:F<150)

* Probably = at least one multicenter RCT supports

Take home #3

- In early, moderate to severe ARDS, consider paralytic and proning.
- Especially watch for ventilator dyssynchrony
What about PEEP in ARDS?

ALVEOLI study
- 549 patients with ARDS (P:F<300)
- Randomized to high or low PEEP

<table>
<thead>
<tr>
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<th>High PEEP</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Death before discharge</td>
<td>25</td>
<td>28</td>
<td>.48</td>
</tr>
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<td>Ventilator free days</td>
<td>14.5</td>
<td>13.8</td>
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*NEJM.* 2004,351: 327-336

Maybe high PEEP helps some in ARDS

- Meta-analysis of 2299 patients in 3 ARDS trials of low vs. high PEEP
- No difference in mortality in all patients
- But! PEEP effects differ with ARDS severity

<table>
<thead>
<tr>
<th>P:F Ratio</th>
<th>60 day hazard: death with high PEEP</th>
<th>P value</th>
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<tbody>
<tr>
<td>&lt;200</td>
<td>.85</td>
<td>.03</td>
</tr>
<tr>
<td>200-300</td>
<td>1.32</td>
<td>.2</td>
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*JAMA.* 2010, 303: 865-873
PEEP in ARDS: Does 1 size fit all?

Driving Pressure and Survival in the Acute Respiratory Distress Syndrome

- 3562 patients in 9 RCTs of ARDS
- Is it volume or pressure that matters?
- Examined the driving pressure ($\Delta P$)
  - $\Delta P = \frac{V_T}{C_{RS}}$
  - If no inspiratory effort $\Delta P = P_{plat} - PEEP$

*NEJM.* 2015, 372: 747-755
PEEP in ARDS: Does 1 size fit all?

PEEP 5

PEEP 12
PEEP in ARDS: Does 1 size fit all?
Constant PEEP, changing $P_{plat}$

Airway Pressure (cm)

RR of death

ATLS Core Curriculum 2016

PEEP in ARDS: Does 1 size fit all?
Constant delta P, rising $p_{Plat}$

Airway Pressure (cm)

RR of death

PEEP in ARDS: Does 1 size fit all?
Constant Pplat, rising PEEP/falling Delta P

Airway Pressure (cm)

PEEP

PEEP (cm of water)

Respiratory compliance

PEEP in ARDS: Titration by esophageal balloon

- Single center RCT
- 61 patients
- PaO₂:FIO₂<300
- Control arm: standard ARDS ventilation
- Trend toward lower mortality
  - ~39 vs 17% p = .06

NEJM. 2008, 359: 2095-2104

Does treatment improve ARDS mortality?

**Definitive**
- Lung protective ventilation

**Probably***
- Neuromuscular blockade (P:F<150)
- Prone positioning (P:F<150)
- High or tailored PEEP

**No (partial list)**
- But! Tailored PEEP had not been tested in an RCT

*Probably = at least one multicenter RCT supports

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A trial of Titrated PEEP in ARDS
the ART study, JAMA 2017

- 1010 pts in 9 countries
- Randomized to standard ARDSNet PEEP vs tailored PEEP
- P:F<200
- 65% had shock

*JAMA. 2017; 318 (14): 1335-1345*
Trial design: recruitment maneuver

- After 500 pts and 3 cardiac arrests
  - 25 x 1 min, 30 x 1 min, 35 x 1 min
  - Start at 23 and go down q 3 min
  - Re-recruit at 35
High/tailored PEEP didn’t help

- Increasing evidence shows that, especially for more severe ARDS, higher PEEP likely helps
- Targeting PEEP to the patient (by doing ΔP titration or esophageal balloon) is intriguing but not yet proven in RCT
- Avoid prolonged, high pressure recruitment manoeuvres
Does treatment improve ARDS mortality?

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<td>High or tail</td>
<td>High or tailored PEEP</td>
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* Probably = at least one multicenter RCT supports

ECMO for the sickest of the sick

- ECMO for severe ARDS: EOLIA trial
- Is ECMO better for severe ARDS?
  - Very severe ARDS, intubated <7 days with:
    - P:F<50 for 3h
    - P:F<80 for 6h
    - pH<7.25 with PCO2 >60 for 6h
  - Above values on 6 ml/kg, PEEP >=10, Pplat<32

*NEJM. 2018, 378: 1965-75*
ECMO (EOLIA trial)

Key points:
- Great adherence to standard of care (90% proned, all paralyzed, 83% inhaled NO or flolan, all low tidal volume prior to enrollment)
- Strict crossover rule!!
  - O2 sat <80% for >6h
  - No irreversible organ damage/chance for survival
- Powered for large absolute risk difference (60% to 40% mortality)

NEJM. 2018, 378: 1965-75

ECMO: EOLIA

Stopped for futility, 249 pts in 6y
35% vs 46% 60d mortality (p=.09)

35 ctrl pts (28%) crossed over to ECMO, 9 after cardiac arrest, 11 on CRRT, 57% mort

NEJM 2018
Does treatment improve ARDS mortality?

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Take home points recapped!

- In early respiratory failure consider high flow
- Low tidal volume, low pressure ventilation is still the #1 maneuver for ARDS mechanical ventilation
  - A LOT of patients meet ARDS criteria
  - We miss it often
- If mod-severe ARDS: paralytic and proning early
- PEEP: Higher probably better, especially in moderate to severe ARDS
  - consider titration to best compliance
- Consider ECMO in the sickest patients