ARDS and Lung Protection

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Overview

• Low tidal volume strategy
• Fluid conservative therapy
• Interventions for refractory hypoxemia
• Interventions for severe respiratory acidosis
• Future directions in ALI/ARDS treatment
• Arguments for low tidal volume strategy in the operating room
INCLUSION CRITERIA: Acute onset of
1. \( \text{PaO}_2/\text{FiO}_2 \leq 300 \) (corrected for altitude)
2. Bilateral (patchy, diffuse, or homogeneous) infiltrates consistent with pulmonary edema
3. No clinical evidence of left atrial hypertension

PART I: VENTILATOR SETUP AND ADJUSTMENT
   - Males = 50 + 2.3 [height (inches) – 60]
   - Females = 45.5 + 2.3 [height (inches) – 60]
2. Select any ventilator mode
3. Set ventilator settings to achieve initial \( V_i = 8 \text{ ml/kg PBW} \)
4. Reduce \( V_i \) by \( 1 \text{ ml/kg} \) at intervals ≤ 2 hours until \( V_i = 6 \text{ ml/kg PBW} \)
5. Set initial rate to approximate baseline minute ventilation (not > 35 bpm)
6. Adjust \( V_i \) and RR to achieve pH and plateau pressure goals below.

OXYGENATION GOAL: \( \text{PaO}_2 \geq 55-80 \text{ mmHg or SpO}_2 \geq 88-95\% \)
Use a minimum PEEP of 5 cm H2O. Consider use of incremental \( \text{FiO}_2/\text{PEEP} \) combinations as shown below (not required) to achieve goal.

Lower PEEP/HIGHER \( \text{FiO}_2 \)

<table>
<thead>
<tr>
<th>( \text{FiO}_2 )</th>
<th>0.3</th>
<th>0.5</th>
<th>0.7</th>
<th>0.9</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td>8</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>( \text{FiO}_2 )</th>
<th>0.9</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>PEEP</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Higher PEEP/LOWER \( \text{FiO}_2 \)

<table>
<thead>
<tr>
<th>( \text{FiO}_2 )</th>
<th>0.3</th>
<th>0.5</th>
<th>0.7</th>
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<tbody>
<tr>
<td>PEEP</td>
<td>5</td>
<td>8</td>
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</tr>
<tr>
<td>PEEP</td>
<td>10</td>
<td>10</td>
<td>10</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>( \text{FiO}_2 )</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEEP</td>
<td>16</td>
</tr>
<tr>
<td>PEEP</td>
<td>20</td>
</tr>
<tr>
<td>PEEP</td>
<td>22</td>
</tr>
</tbody>
</table>
**PLATEAU PRESSURE GOAL:** ≤ 30 cm H₂O
Check Pplat (0.5 second inspiratory pause), at least q 4h and after each change in PEEP or V̇.
- **If Pplat > 30 cm H₂O:** decrease V̇ by 1 ml/kg steps (minimum = 4 ml/kg).
- **If Pplat ≤ 25 cm H₂O and V̇ < 6 ml/kg:** increase V̇ by 1 ml/kg until Pplat > 25 cm H₂O or V̇ = 6 ml/kg.
- **If Pplat < 30 and breath stacking or dys-synchrony occurs:** may increase V̇ in 1 ml/kg increments to 7 or 8 ml/kg if Pplat remains ≤ 30 cm H₂O.

**pH GOAL:** 7.30-7.45
- **Acidosis Management:** (pH < 7.30)
  - If pH 7.15-7.30: increase RR until pH ≥ 7.30 or PaCO₂ ≤ 25
    - (Maximum set RR = 35).
  - **If pH < 7.15:** Increase RR to 35.
    - If pH remains < 7.15, V̇ may be increased in 1 ml/kg steps until pH > 7.15 (Pplat target of 30 may be exceeded).
    - May give NarCO₂.
- **Alkalosis Management:** (pH > 7.45) Decrease vent rate if possible.

**I:E RATIO GOAL:** Recommend that duration of inspiration be ≤ duration of expiration.
Comparison of two fluid-management strategies in ALI

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Conservative Strategy</th>
<th>Liberal Strategy</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death at 60 days (%)</td>
<td>25.5</td>
<td>28.4</td>
<td>0.30</td>
</tr>
<tr>
<td>Ventilator-free days from day 1 to day 28</td>
<td>14.6±0.5</td>
<td>12.1±0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU-free days†</td>
<td>0.9±0.1</td>
<td>0.6±0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Days 1 to 28</td>
<td>13.4±0.4</td>
<td>11.2±0.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Simplified Fluid Conservative Protocol

- Patient must be out of shock for at least 12 hrs
- Target CVP < 4 with urine output ≥ 0.5 ml/kg/hr
- Net even fluid balance over first seven days

Therapies for Severe Acute Lung Injury

- High PEEP
- Recruitment maneuvers
- Alternative Ventilator Strategies:
  - High-frequency oscillatory ventilation
- Inhaled Nitric Oxide
- Glucocorticoids
- Prone Positioning
High versus standard PEEP

• ARDSnet ALVEOLI trial, NEJM 2004
• 2 trials on standard vs. high PEEP (JAMA 2008)
  – Multifaceted Lung Open Ventilation study (LOV)
  – Positive End-expiratory Pressure Setting in Adults with ALI (EXPRESS)
• No difference in mortality in any of these three trials

Recruitment Maneuvers

• What is a recruitment maneuver?
  – Sustained inspiratory hold (~30-60 seconds) at higher than normal airway pressures
  – Sustained pressure = 40-45 cm H2O
• What is the goal?
  – to recruit atelectatic/flooded alveoli
  – Increase lung capacity
• What are the potential adverse effects?
  – Hypotension
  – Barotrauma
  – Requirement for sedation +/- paralysis
• Not recommended or discouraged based on current evidence

High Frequency Oscillatory Ventilation (HFOV)

• Oscillating piston (180-900 x/minute)
  – Very small tidal volumes (1-2.5 ml/kg)
• High mean airway pressure
  – Goal is to recruit atelectatic lung segments and improve oxygenation
• May require heavy sedation +/- paralysis
• Can lead to hypotension from high intrathoracic pressures
• No confirmed mortality benefit
• Skilled health care team is necessary (MD’s, RT’s, nursing)
Inhaled Nitric Oxide

- Selective pulmonary vasodilator
- Delivered only to ventilated alveolar units
- Improvement in V/Q matching and PaO2/FiO2 ratio

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>Nitric oxide</th>
<th>Control</th>
<th>Ratio of increase (%)</th>
<th>Weight</th>
<th>Ratio of increase (%)</th>
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<tbody>
<tr>
<td>Gray **</td>
<td>11</td>
<td>10</td>
<td>11</td>
<td>3.8</td>
<td>0.93 (0.64 to 1.34)</td>
<td></td>
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<tr>
<td>Schumacher **</td>
<td>9</td>
<td>10</td>
<td>9</td>
<td>5.5</td>
<td>1.28 (0.84 to 1.56)</td>
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<tr>
<td>Delight **</td>
<td>120</td>
<td>57</td>
<td>120</td>
<td>2.9</td>
<td>1.27 (0.84 to 1.56)</td>
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<tr>
<td>Ahluwalia **</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>8.3</td>
<td>1.34 (0.91 to 1.55)</td>
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</tr>
<tr>
<td>Teich **</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>8.4</td>
<td>1.34 (0.91 to 1.55)</td>
<td></td>
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<tr>
<td>Olney **</td>
<td>49</td>
<td>30</td>
<td>49</td>
<td>11.9</td>
<td>1.34 (0.91 to 1.55)</td>
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<tr>
<td>Lucey **</td>
<td>78</td>
<td>46</td>
<td>78</td>
<td>21.1</td>
<td>1.34 (0.91 to 1.55)</td>
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<tr>
<td>Mafe **</td>
<td>8</td>
<td>6</td>
<td>8</td>
<td>4.7</td>
<td>1.34 (0.91 to 1.55)</td>
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<tr>
<td>Pat **</td>
<td>11</td>
<td>6</td>
<td>11</td>
<td>4.1</td>
<td>1.34 (0.91 to 1.55)</td>
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<tr>
<td>Total</td>
<td>319</td>
<td>336</td>
<td>319</td>
<td>10.0</td>
<td>1.34 (0.91 to 1.55)</td>
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Effect of nitric oxide on mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Deaths/patients randomized</th>
<th>Nitric oxide</th>
<th>Control</th>
<th>Risk ratio</th>
<th>Weight</th>
<th>Risk ratio</th>
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<tbody>
<tr>
<td>Delight **</td>
<td>35/120</td>
<td>17/57</td>
<td>18/63</td>
<td>11.2</td>
<td>0.99 (0.40 to 2.09)</td>
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<tr>
<td>Mafe **</td>
<td>11/19</td>
<td>9/20</td>
<td>10/29</td>
<td>6.0</td>
<td>1.21 (0.67 to 2.19)</td>
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<tr>
<td>Teich **</td>
<td>9/15</td>
<td>8/15</td>
<td>10/15</td>
<td>6.7</td>
<td>1.32 (0.68 to 2.55)</td>
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</tr>
<tr>
<td>Olney **</td>
<td>42/95</td>
<td>35/87</td>
<td>45/105</td>
<td>22.5</td>
<td>1.32 (0.68 to 2.55)</td>
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<tr>
<td>Lucey **</td>
<td>68/96</td>
<td>44/105</td>
<td>72/115</td>
<td>10.1</td>
<td>1.32 (0.68 to 2.55)</td>
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</tr>
<tr>
<td>Mafe **</td>
<td>4/36</td>
<td>3/76</td>
<td>5/109</td>
<td>1.5</td>
<td>1.52 (0.40 to 4.60)</td>
<td></td>
</tr>
<tr>
<td>Pat **</td>
<td>3/10</td>
<td>4/29</td>
<td>7/109</td>
<td>3.4</td>
<td>1.52 (0.40 to 4.60)</td>
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<tr>
<td>Taylor **</td>
<td>4/133</td>
<td>2/76</td>
<td>6/193</td>
<td>5.6</td>
<td>1.52 (0.40 to 4.60)</td>
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<tr>
<td>Total</td>
<td>527/909</td>
<td>509</td>
<td>527</td>
<td>100.0</td>
<td>1.52 (0.40 to 4.60)</td>
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Prone positioning

- Better matching of ventilation and perfusion
- Opening of dependent collapsed lung segments
- Improves oxygenation in about 70% of patients
- Now at least four large RCT’s showing no improvement in mortality
- Technically challenging

ECMO

- Veno-venous circuit that relieves lungs from role in gas exchange
- Oxygenation and removal of CO2
- Requires large bore IV access and anticoagulation
Severe ARDS:
- Lung injury score > 3, hypercapnic acidosis with pH<7.2
- Randomized to usual care or transfer to an ECMO center
- Intervention group had lower rate of composite endpoint of death/severe disability at 6 months (47 vs 63%, p=0.03)
  - Unclear whether ECMO improved outcomes versus other aspects of care

When is ECMO Considered?
- No firm criteria
- CESAR trial criteria:
  - Lung injury score > 3, or
  - Hypercapnic respiratory failure with pH<7.2
- Other criteria:
  - Respiratory failure judged to be reversible
  - Early in course of disease
  - No contraindication to anticoagulation

Is there a role for steroids?
- Corticosteroids have been demonstrated ineffective in prevention of ARDS or treatment of early ARDS
  (Sprung NEJM 1984; Bernard NEJM 1997; Luce ARRD 1988)
- Late Steroid Rescue Study (LaSRS, NEJM 2006) focused on patients with persistent ARDS
- Results of LaSRS
  - Improvement in PaO2:FiO2 ratio but no difference in overall mortality
  - More neuromyopathy with methylprednisolone
  - No difference in serious infections
Cisatracurium for Early Severe ARDS

- N=340
- P:F ratio < 150 on PEEP ≥ 5
- Within 48 h of presentation
  - Cisatracurium for 48 h
    - Bolus followed by infusion of 37.5 mg/hr
  - HR for death 0.68 (0.48-0.98, p=0.04)
    - After adjustment for baseline imbalances


Treatment of Severe Respiratory Acidosis

- Increase respiratory rate
- Buffer therapy
  - THAM vs. bicarbonate
- Continuous renal replacement therapy
- ECMO

Kallet et al, AJRCCM 2000

Ventilator associated lung injury in patients without lung injury at the onset of mechanical ventilation

- Retrospective cohort study
- 447 patients who received mechanical ventilation for >48 hours
- Risk factors independently associated with the development of ARDS included the size of the tidal volume during the first day, receipt of transfused blood products, a history of restrictive lung disease, and acidemia
- Short patients and women received statistically larger tidal volumes than men

Gajic et al, Crit Care Med 2004
Ventilator Settings as a risk factor for ARDS in mechanically ventilated patients

- Retrospective study of 3,261 patients who required >48 hours of mechanical ventilation
- 205 out of 3,261 patients developed ARDS
- Development of ARDS was independently associated with a high initial VT setting, high peak airway pressures, and the use of high PEEP

Gajic et al, Intensive Care Med 2005

Influence of Low Tidal Volume Ventilation on Time to Extubation in Cardiac Surgical Patients

- Single center randomized controlled trial
- 149 patients undergoing elective cardiac surgery
- Mean ventilation time not significantly different
- Higher proportion in low VT group free of ventilation at 6 hours
- Fewer patients in low VT group required reintubation

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Summary

- Low tidal volume ventilation and fluid conservative treatment are the mainstays of treatment
- For refractory hypoxemia, patients may receive alternative/rescue therapies such as higher PEEP, recruitment maneuvers, high frequency oscillatory ventilation, and/or nitric oxide
- Patients may receive neuromuscular blockade in severe ARDS
- If available, ECMO is a reasonable option for refractory hypoxemia or severe respiratory acidosis
- Consider lower tidal volumes at PBW in mechanically ventilated patients in the operating room