Basics of Mechanical Ventilation

A. Ventilator Associated Lung Injury

1. What is ventilator associated lung injury (VALI)? Although mechanical ventilation can be life saving, it can also injure the lung as well as contribute to systemic inflammation. There are four major mechanisms of VALI: oxygen toxicity, macrobarotrauma, microbarotrauma, and repeated alveolar collapse and expansion (RACE).
   a. What is oxygen toxicity? Traditionally, prolonged exposure to high levels of FIO2 is thought to be injurious to the lung. There is no universal agreement regarding a “safe” level or duration of high FIO2 exposure. However, it is commonly recommended to reduce the FIO2 to <60% as soon as possible.
   b. What is macrobarotrauma? Macrobarotrauma refers to a form of lung injury caused by ventilator-induced overdistention of a vulnerable lung unit that results in pneumothorax, pneumomediastinum, or subcutaneous emphysema. Typically, macrobarotrauma manifests itself in clinically evident ways so that a clinician can readily appreciate its occurrence at the bedside.
   c. What is microbarotrauma? Microbarotrauma, also termed volutrauma, refers to a form of lung injury caused by ventilator-induced overdistention that results in inflammatory injury of vulnerable lung units. Because there are no immediately overt consequences such as a pneumothorax, the occurrence of microbarotrauma is not typically apparent at the bedside. In general, excessive airway pressures and lung volumes should be avoided in order to minimize the risks of macro- and microbarotrauma.
   d. What is RACE injury? This type of lung injury, also called atelectrauma, is thought to occur from repeated opening and closing of collapsed alveoli. Many patients with respiratory failure have regions of the lung that are collapsed. The delivery of tidal volume during inspiration may force open the collapsed regions only for it to collapse again with exhalation. This repetitive pattern of lung collapse and forced expansion is believed to cause alveolar injury. In general, sufficient positive end expiratory pressure should be applied in order to minimize atelectasis and avoid the risk of RACE injury.

2. Pressure Volume Curve (PV Curve)
   a. What is the shape of the PV curve? In theory, the PV curve of the respiratory system is sigmoidal in shape. In general, as more pressure is applied to the lung, the total volume of the lung increases correspondingly. However, at both extremes of the curve, the slope flattens. At high volumes, despite increasing pressure, the volume does not correspondingly increase because of the physical limits imposed by the lung and chest wall. At low volumes, despite decreasing pressure, the volume does not correspondingly decrease because of the physical limits imposed by the chest wall and the elastic recoil of the lung. This is similar to the concepts of total lung capacity and residual volume measured during pulmonary function testing.
   b. What are inflection points? Maximal changes in the slope of the curve occur at points called the upper inflection point (UIP) and the lower inflection point (LIP). In theory, mechanical ventilation beyond the UIP may cause macro- and microbarotrauma due to alveolar overdistention. On the other hand, mechanical ventilation below the LIP may result in atelectasis of some alveoli. If the atelectatic lung units undergo repeated cycles of opening and collapse with each tidal breath, RACE injury may occur.
   c. Suppose a patient with PV curve above is being ventilated as follows: FIO2 50%, TV 0.5 L, rate 10, PEEP 5. [Assume patient is sedated. Also assume the following coordinates: point A (P 5, V 2.7); point B (P 10, V 3.2).]

1) At the end of expiration, what is the pressure? The end expiratory pressure is called the positive end expiratory pressure, or PEEP. Since PEEP is set at 5 in this case, by definition, the pressure at end expiration is 5 cm of H2O.

2) What is the end expiratory volume (EEV)? In this example, PEEP of 5 is associated with an EEV of 2.7 L, which is represented by point A.

3) What is the end inspiratory volume (EIV)? Since the EEV is 2.7 L and a TV of 0.5 L is being added during inspiration, the EIV is 3.2 L.

4) At end inspiration, what is the pressure? The end inspiratory pressure is also known as the plateau pressure (Ppl). In this example, the EIV of 3.2 L is associated with Ppl of 10 cm, which is represented by point B.

5) In this example, the ventilator is set to deliver 0.5 L of 50% O2, which takes the patient from point A to end expiration to point B at end inspiration. Since ventilating from A to B violates neither the LIP nor the UIP, patient is not at high risk for RACE or barotrauma injuries.
d. Suppose that another patient undergoes colectomy for diverticular abscess but remains intubated post-operatively because of hemodynamic instability. Next day, patient develops multisystem organ failure, including ARDS.

1) Which of the two PV curves shown on the right likely represents the immediate post-operative period? Curve 1. Which likely represents the PV curve on the next day after ARDS has developed? Curve 2. Notice that with ARDS, the PV curve has shifted both downward and to the right. This is because ARDS is associated with variable amounts of atelectasis which cause the PV curve to shift downward. In addition, inflammation and edema associated with ARDS decreases the lung compliance, which rotates the PV curve clockwise.

2) What changes are expected if the patient is on volume cycled ventilation with 50% FIO2, TV 0.4 L, Rate 10, PEEP 8? [Assume patient is sedated. Also assume the following coordinates: point A (P 8, V 2.5); point B (P 15, V 2.9); point C (P 8, V 2.3); point D (P 22, V 2.5); point E (P 35, V 2.7); point F (P 50, V 2.9).]

a) Before patient had developed ARDS (curve 1), PEEP of 8 is associated with an EEV of 2.5 L (point A). Since TV is set at 0.4 L, the EIV is 2.9 L, which is associated with Ppl of 15 (point B).

b) However, after the patient develops ARDS (curve 2) on the same ventilator settings, PEEP of 8 is now associated with EEV of 2.3 L (point C). Since TV is still set at 0.4 L, the EIV is 2.7 L, which is associated with Ppl of 35 (point E). Notice this Ppl is now much higher than the previous value of 15.

3) Patient is still on 50% FIO2, TV 0.4 L, Rate 10, PEEP 8. ABG on these settings are as follows: PO2 100, PCO2 60, pH 7.24. In theory, what type of VALI is this patient most at risk? The ventilator delivers 0.4 L of 50% O2 and takes the patient from point C at end expiration to point E at end inspiration on curve 2. With the FIO2 <60%, patient is not at high risk for oxygen toxicity. However, since ventilation from C to E violates the LIP but not the UIP, patient is primarily at risk for RACE injury.

4) A change in ventilator settings is being considered. For each potential change below, complete the table that describes the ventilatory pattern. [Assume the following coordinates: C (P 8, V 2.3); D (P 22, V 2.5); E (P 35, V 2.7); F (P 50, V 2.9).]

<table>
<thead>
<tr>
<th>#</th>
<th>FIO2</th>
<th>Rate</th>
<th>TV</th>
<th>PEEP</th>
<th>Expiration Point &amp; Inspiration Point</th>
<th>Ppl</th>
<th>PCO2</th>
<th>O2 Toxicity</th>
<th>Barotrauma</th>
<th>RACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50%</td>
<td>10</td>
<td>0.4 L</td>
<td>8</td>
<td>C to E</td>
<td>35</td>
<td>60</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>50%</td>
<td>10</td>
<td>0.6 L</td>
<td>8</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>3</td>
<td>50%</td>
<td>10</td>
<td>0.2 L</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>50%</td>
<td>10</td>
<td>0.4 L</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a) Setting #1 – This setting ventilates the patient from C to F and the new Ppl will be 50. The PCO2 will be lower since the minute ventilation increases from 4 to 6 lpm. Since this setting violates both the LIP and the UIP, patient is now at theoretical risk for both barotrauma and RACE injuries.

b) Setting #2 – This setting ventilates the patient from C to D and the new Ppl will be 22. The PCO2 will be higher since the minute ventilation decreases from 4 to 2 lpm. Since this setting still violates the LIP, but not UIP, patient is still primarily at risk for RACE injury.

c) Setting #3 – This setting ventilates the patient from D to E and the new Ppl will be 35. The PCO2 will be higher since the minute ventilation decreases from 4 to 2 lpm. Since this setting still violates the UIP, patient is theoretically not at risk for any type of VALI.

d) Setting #4 – This setting ventilates the patient from D to F and the new Ppl will be 50. The PCO2 will be unchanged because the minute ventilation does not change. Since this setting violates the UIP but not the LIP, patient is primarily at risk for barotrauma.

e) Which ventilator setting is best in terms of ABG results? Ventilator setting #1 is the “best” in terms of ABG results because it is the only setting that lowers the PCO2. However, notice that this “best” ventilator setting is best in terms of ABG results is actually the worst in terms of the overall risk for VALI.

f) Which ventilator setting is best in terms of minimizing the risk of VALI? Since ventilator setting #3 violates neither the LIP nor the UIP, it offers the lowest theoretical risk for VALI. However, notice that this setting will actually make the ABG results worse. This paradox is frequently encountered, especially among those with ARDS or severe obstructive lung disease. As discussed below, current evidence suggests that avoiding VALI is a more important goal than achieving normal ABGs.
3. PV Curve and the Stress Index
   a. **Why is the PV curve not used routinely?** The technical details for determining the PV curve are beyond the scope of this chapter. Nevertheless, it is important to note that PV curve determination is labor intensive, difficult to reproduce, and not without risk to the patient. As of now, there is still no simple, practical method of determining the PV curve at the bedside that has won universal acceptance. Thus, PV curve is not determined routinely in the clinical setting, and it remains primarily a research tool. Nevertheless, the physiologic concepts behind the PV curve are still extremely useful in understanding mechanical ventilation and its associated risks of lung injury.

   b. **What is the equation of motion?** Airway pressure during any point of inspiration ($P_{aw}$) is the sum of the starting airway pressure (i.e. PEEP), pressure due to the resistance of the airway ($P_R$), and the pressure due to the compliance of the respiratory system ($P_C$): $P_{aw} = PEEP + P_R + P_C$. Given that $P_R$ is a function of inspiratory flow ($F$) and airway resistance ($R$) and $P_C$ is a function of the lung volume ($V$) and respiratory system compliance ($C$), $P_{aw}$ can be written according to the equation of motion as follows: $P_{aw} = PEEP + FR + V/C$.

   c. **What is the stress index ($b$)?** If tidal volume is delivered at a constant flow rate (i.e. square wave form), then flow, resistance and PEEP can be combined as one constant $P_0$, where $P_0 = FR + PEEP$. Then the equation of motion can be reduced to: $P_{aw} = mV + P_0$, where $m = 1/C$ and $b$ is the stress index. As shown in the graphs to the right, if $b < 1$, the shape of the pressure-time curve during constant flow portion is concave down; if $b = 1$, the curve is linear; and if $b > 1$, the curve is concave up.

1) **What is the relationship between the stress index and the PV curve?** Under normal circumstances, the PEEP, the compliance and the airway resistance are not expected to change during inspiration. If the inspiratory flow rate is constant (i.e. square wave flow), $V$ rises linearly during inspiration. Since $V$ rises linearly, $P_{aw}$ also rises linearly and the equation takes the form of a straight line: $P_{aw} = mV + P_0$, where $b = 1$. This situation is expected when the breath is being delivered between the two inflection points where the PV curve is linear and the compliance of the respiratory system does not change significantly during inspiration. Therefore, a linear pressure-time curve ($b = 1.0$) suggests that the breath is being delivered between the two inflection points, theoretically free from RACE and volutrauma risks. On the other hand, if the $P_{aw}$ curve is concave down (i.e. $b < 1$), the compliance must be improving during inspiration which occurs if the LIP is being traversed, theoretically risking RACE injury. If the curve is concave up (i.e. $b > 1$), the compliance must be decreasing during inspiration which occurs when the UIP is being traversed, theoretically risking volutrauma.

2) **Can the stress index be used to detect hyperinflation and RACE?** Grasso. CCM 2004; 32: 1018-27. In an animal model of ARDS, PEEP and TV were adjusted so that the stress index, $b$, was less than 1, equal to 1, or greater than 1. CT scans were obtained at end-expiration (black lines) and again at end-inspiration (gray lines) to estimate the degree of overdistention and RACE occurring at each stress index value. As predicted by the stress index model, there was no significant hyperinflation and minimal RACE when $b = 1$ (left graph). However there was substantial RACE when $b < 1$ (middle graph) while significant hyperinflation was observed when $b > 1$ (right graph).
4. **What is the evidence for VALI?**
   
a. Animal Data - Dreyfuss. American Review of Respiratory Diseases 1988; 137: 1159-1164. This PRCT of 33 rats compared the effects of various ventilatory strategies on several measures of lung injury: extravascular lung water (Q, cc/kg), dry lung weight (DLW, g/kg of body weight), and albumin space (AS, %). Rats were anesthetized, trached, paralyzed, and ventilated for 20 minutes.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>High Pressure / High Volume</th>
<th>Low Pressure / High Volume (Neg. Pressure)</th>
<th>High Pressure / Low Volume (Chest Bound)</th>
<th>High Pressure / High Volume with PEEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure cm H$_2$O</td>
<td>7</td>
<td>45</td>
<td>7</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>TV cc/kg</td>
<td>13</td>
<td>40</td>
<td>44</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>PEEP</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Q cc/kg</td>
<td>2.8</td>
<td>7.0</td>
<td>8.5</td>
<td>2.4</td>
<td>3.9</td>
</tr>
<tr>
<td>DLW g/kg</td>
<td>0.72</td>
<td>0.95</td>
<td>1.10</td>
<td>0.60</td>
<td>0.75</td>
</tr>
<tr>
<td>AS</td>
<td>13%</td>
<td>70%</td>
<td>80%</td>
<td>10%</td>
<td>35%</td>
</tr>
</tbody>
</table>

1) *What was the effect of high pressure and high volume?* Compared to the control rats, mechanical ventilation with high pressure and high volume resulted in significant VALI as measured by substantial increases in Q, DLW, and AS.

2) *Which is more important for VALI, high pressure or high volume?* To test whether VALI is caused primarily by high pressure (i.e. barotrauma), high volume (i.e. volutrauma), or both, rats were also mechanically ventilated with low-pressure-high-volume settings (i.e. “negative pressure ventilation”) and high-pressure-low-volume settings (i.e. “chest bound”). In the “chest bound rats” the markers of lung injury were minimally elevated. In contrast, the “negative pressure rats” experienced substantial VALI. Thus, the relevant mechanism of lung injury appears to be volutrauma from physical overstretching of the alveoli, rather than high pressure per se.

3) *What was the effect of PEEP in this study?* Addition of PEEP moderated the degree of lung injury. PEEP presumably decreased atelectasis, ventilated the animals above the LIP, and protected against RACE injury.

b. Human Data – Ranieri. JAMA 1999; 282(1): 54-61. This PRCT of 37 ARDS patients (intubated within 8 hours of the study) compared conventional strategy vs. lung protective strategy and measured various markers of inflammation at 0, 24 and 36 hours. Conventional strategy adjusted the TV for PCO$_2$ goal of 35-40 and the PEEP for best oxygen delivery (i.e. best ABG goal). On the other hand, lung protective strategy adjusted the TV to keep below UIP and the PEEP to keep above LIP (i.e. avoid VALI goal).

1) *What was the effect of the two strategies on the markers of inflammation?* With conventional strategy, the markers of inflammation in the lung (BAL neutrophils, IL-1, TNF-α, IL-6, IL-8) and plasma (TNF-α, IL-6, IL-8) all increased with time. In contrast, for patients treated with LPS, these same markers decreased or did not substantially change.

2) *What was the effect of the two strategies on clinical outcome?* The number of ventilator free days increased with LPS. There was also a trend toward lower mortality with LPS, but the difference was not statistically significant.

<table>
<thead>
<tr>
<th></th>
<th>CS</th>
<th>LPS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TV (cc/kg)</td>
<td>11.1</td>
<td>7.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PEEP</td>
<td>6.5</td>
<td>14.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Ppl</td>
<td>31.0</td>
<td>24.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Ventilator Free Days</td>
<td>4</td>
<td>12</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>28-Day Mortality</td>
<td>58%</td>
<td>38%</td>
<td>NS</td>
</tr>
</tbody>
</table>

c. *Are patients vulnerable to VALI if they do not have ARDS?* In contrast to those with ARDS, patients without ARDS are thought to be at low risk for VALI because the use of traditional TV and PEEP are less likely to violate the UIP or the LIP. This is because their PV curve is not flattened to the same degree as those with ARDS. However, recent studies challenge this thought.

1) Zupancich. Journal of Thoracic & Cardiovascular Surgery 2005; 130: 378-83. In a PRCT of 40 patients being disconnected from cardiopulmonary bypass following elective cardiac bypass surgery, mechanical ventilation with high TV and low PEEP (10-12 ml/kg and PEEP 2-3) for 6 hours was associated with significantly higher serum levels of IL-6 and IL-8 compared to mechanical ventilation with low TV and high PEEP (8 ml/kg and PEEP 10).
2) Mascia. JAMA 2010; 304: 2620-7. In a PRCT of 118 brain dead patients who were potential lung donors, conventional ventilatory strategy (TV 10-12 ml/kg, PEEP 3-5 cm H₂O, apnea testing via disconnection from the ventilator) was compared to lung protective strategy (TV 6-8 ml/kg, PEEP 8-10 cm H₂O, apnea testing via continuous positive airway pressure circuit). The number of patients who met lung donation eligibility criteria was significantly higher after lung protective strategy compared to conventional strategy (95% vs. 54%, P < 0.001).

d. These studies demonstrate that mechanical ventilation can in of itself cause significant lung injury as well as contribute to systemic inflammation. In fact, VALI appears to occur early in the course of mechanical ventilation, i.e. within the first 6-36 hours. Therefore, minimizing such lung injury as early as possible could lead to survival benefit in patients with respiratory failure.

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