Mechanical Ventilation in Acute Respiratory Distress Syndrome

Time Heals All Wounds, or Does It?

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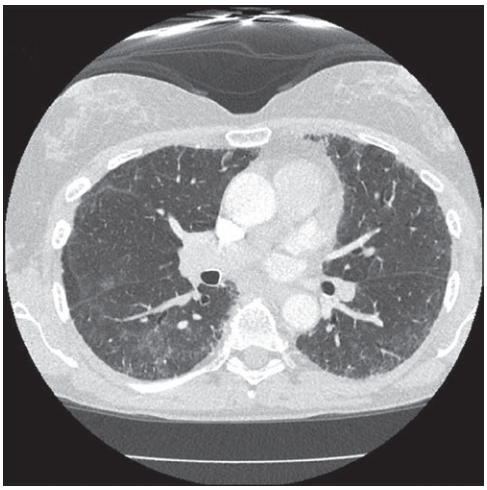
Acute respiratory distress syndrome (ARDS), characterized by the acute onset of hypoxemia (Pao_2/Fio_2 less than or equal to 300), bilateral pulmonary radiographic opacities, and diffuse inflammatory-induced pulmonary capillary leakage,[1] is a critical public health issue. There are more than three million patients per year with ARDS receiving mechanical ventilation,[2] and their mortality rate is very high, ranging from about 30% to 40%.[3]

Over the last 25 yr, a substantial body of literature has clearly demonstrated that this high mortality rate is in part attributable to the injurious effects of mechanical ventilation, so-called ventilator-induced lung injury.[4] Although significant progress has been made in reducing ventilator-induced lung injury and improving patient outcomes, current lung protective ventilatory strategies may still be associated with high risk of ventilator-induced lung injury, especially in patients with more severe ARDS.[5] As such, increased understanding of the pathophysiologic mechanisms mediating ventilator-induced lung injury, through studies such as the one by Felix *et al.*[6] in this issue of the Journal, is important to help design optimal ventilatory strategies,[7] and potentially improve outcomes.

The two major mechanisms that are thought to mediate ventilator-induced lung injury are regional alveolar overdistension, leading to barotrauma and volutrauma, and tidal airway opening and collapse, so-called atelectrauma.[4] Both of these mechanisms of injury can lead to biotrauma with release of mediators into the lung, and then into the systemic circulation, which in turn can cause end-organ dysfunction and death.[8] Other factors which are thought to play a role in ventilator-induced lung injury are respiratory rate,[9] pulmonary blood flow,[10] and development of pendelluft,[11] although the precise contributions of each of the mechanisms are unclear.



"[Would] lung injury induced by high tidal volume ventilation [in ARDS]... be less if that high tidal volume was reached by gradually increasing tidal volume over time[?]"

To minimize ventilator-induced lung injury, current clinical guidelines recommend the use of prone position in moderate to severe ARDS, and limiting tidal volume and airway pressures in all patients. In addition, the guidelines suggest that higher positive end-expiratory pressures (PEEP) may be beneficial in moderate and severe ARDS.[12] However, the optimal reduction of airway pressure or tidal volume, or the optimal end-expiratory pressure and volume to prevent ventilator-induced lung injury and maximize survival, is not known, and crucial pathophysiological questions remain unanswered: Is it total lung volume or tidal volume that's important? What is the optimal PEEP? Does the presence of lung inhomogeneity change the relationship between these critical variables? Is driving pressure or mechanical power delivered to the lung the key variable?

Within the context of this fascinating and important field of research, Felix *et al.*[6] have published an interesting study addressing a novel mechanism of ventilator-induced lung injury. The authors address the hypothesis that the lung injury induced by high tidal volume ventilation would

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be less if that high tidal volume was reached by gradually increasing tidal volume over time. The concept is that if the pulmonary extracellular matrix as well as epithelial and endothelial cells had time to adapt to the increased stretch, the injury would be less.

In an experimental model of mild ARDS induced by intratracheal administration of lipopolysaccharide, the authors randomized rats to receive mechanical ventilation for a total of 2 h as follows: (1) *Negative Control Group*: low tidal volume (6 ml/kg) for 2 h, (2) *No Adaptation Group* (positive control): 6 ml/kg for 1 h followed by an abrupt increase to high tidal volume (22 ml/kg) for 1 h, (3) *Shorter Adaptation Group*: 6 ml/kg for 30 min followed by a slow progressive increase over 30 min to 22 ml/kg, then maintained at 22 ml/kg for 1 h, and (4) *Longer Adaptation Group*: Gradual increase from 6 ml/kg to 22 ml/kg over 60 min, then maintained for 1 h at 22 ml/kg. They found that the *Shorter Adaptation Group* had significantly less damage than the *No Adaptation Group* in a number of variables, including diffuse alveolar damage, interstitial edema, alveolar inhomogeneity, significantly less mRNA lung tissue expression of interleukin 6 (a biomarker for inflammation), less amphiregulin (a biomarker for mechanical pulmonary stretch), and less matrix metalloproteinase 9 (a biomarker of extracellular matrix damage).

These results are generally in accord with previous studies that have addressed the impact of slow increases in PEEP on lung recruitment and lung injury. Silva *et al.*[13] demonstrated in an experimental model of acute lung injury that stepwise recruitment maneuvers were associated with less pulmonary injury compared with sustained inflations at constant airway pressure. Chiumello *et al.*[14] demonstrated a time-dependent impact of PEEP on oxygenation in patients with ARDS, such that when PEEP was increased from 5 to 10 to 15 cm H_2O the new equilibrium of gas exchange was not reached even after 60 min, whereas adaptation was faster during decremental PEEP changes.

In essence, it is possible that relatively slow increases in tidal volume as used by Felix *et al.*[6] could have led to recruitment of lung units during the slow increases in tidal volume, thus gradually decreasing lung inhomogeneities, and hence decreasing the stress and strain during and at the end of the gradual increase in tidal volume.

Another interesting hypothesis potentially explaining the importance of time in maximizing lung adaptation to high stress and strain relates to the ability of the lung tissue to repair itself relatively quickly, as nicely demonstrated in a number of experimental studies.[15] Stress adaptation may be viewed as a highly coordinated reorganization within and between cytoskeletal networks, cellular plasma and endomembrane stores, and the supporting lung matrix. These events occur on a subsecond timescale and are integral to the pathogenesis of ventilator-induced lung injury.[16] Although it is convenient to consider ventilator-induced lung injury as the result of having exceeded some physical injury threshold, there are undoubtedly complex nonlinear interactions between physical input amplitude and frequency, and the temporal expressions of local and systemic responses.

So far, all of this makes for a very good story. However, there is one aspect of Felix *et al.*'s study which is very difficult to explain. According to the mechanisms described above, the *Longer Adaptation Group*, which should have had similar or less injury than the *Shorter Adaptation Group*, had *greater* injury, and in fact had injury similar to those animals who received the abrupt increase in tidal volume. The authors suggest that this may have been because the *Longer Adaptation Group* had a greater cumulative transfer of power (area under the curve of power *vs.* time) over the 2-hour period compared with the *Shorter Adaptation Group*. However, if this were the critical variable, then the *No Adaptation Group* should have had the least injury of any of the intervention groups—but it did not. In addition, if the cumulative transfer of power is indeed the critical variable, then over time the impact of any adaptation strategy would eventually become insignificant.

Given this unexpected finding, it is difficult to make direct clinical inferences from this work. It is also unclear whether this adaptation to a progressive increase in tidal volume would occur in humans who have larger lungs, and diverse mechanisms and severities of underlying injury.

The study by Felix *et al.*[6] is intriguing, shining a spotlight on a mechanism of lung injury that has not received a great deal of investigation. And, as with many intriguing studies, it raises more questions than it answers.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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