ARDS – Maintaining gas exchange while limiting iatrogenic lung injury: A delicate balance

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Mechanical ventilation is a life-saving therapy for many patients with acute respiratory failure. However, over the past ~20 years, it has become increasingly apparent that mechanical ventilation can have serious adverse consequences, including increased risk of nosocomial pneumonia, impaired cardiac function, and ventilator-induced lung injury (VILI)1,2. This iatrogenic nature of mechanical ventilation is particularly problematic for patients with the Acute Respiratory Distress Syndrome (ARDS), where mechanical ventilation can be a major factor leading to the death of some patients. This brief review will summarize some key concepts related to our increasing understanding of the iatrogenesis associated with mechanical ventilation, and describe the importance of lung protective ventilation for ARDS patients as well as for non-ARDS patients.

In the 1960’s maintenance of normal PaCO$_2$ and PaO$_2$ were viewed as the critical goal of mechanical ventilation. Anesthesiologists realized that patients in the operating room developed atelectasis and hypoxemia if they were ventilated with small tidal volumes4. To solve this problem, they started using ventilation strategies with very high tidal volumes to re-open those regions of the lung that were collapsed at end-expiration. Clinicians and researchers saw this as beneficial because large tidal volume (VT) ventilation reduced ventilation-perfusion mismatch, meaning there was less need for high oxygen fractions. ICUs at the time were largely run by anesthesiologists, and thus the high VT strategy was used outside the operating room for patients with acute respiratory failure. The thought was that ARDS patients, hypoxemic to start, would similarly suffer from atelectasis and worsening hypoxemia.

Despite sporadic articles in the 1960s and ’70s (e.g. Webb and Tierney) describing the harm of large tidal volumes in animals, this concept was not adopted by clinicians. At the time, getting the blood gases right was the imperative. For example, in 1979 the late Roger Bone published an abstract in which he investigated factors associated with pulmonary barotrauma. 40% of patients had severe barotrauma: the mean VT used was 22±4 ml/kg based on measured body weight!

In the last two decades animal research increasingly and convincingly demonstrated that high tidal volumes could induce VILI. In the late 1980s Dreyfuss and colleagues determined that lung stretch was a critical factor leading to VILI; they coined the term volutrauma to highlight the fact that it was not the airway pressure per se that was important, but the lung stretch4. In the 90’s we demonstrated that ventilatory strategies that allowed recruitment and de-recruitment of lung units could lead to significant lung injury including development of hyaline membranes7. In 1997, we identified a mechanism of injury that we called biotrauma, i.e., the biological consequences associated with mechanical ventilation6. We showed that injurious forms of ventilation, i.e. those that promote atelectrauma and/or over-distension could lead to release of mediators in the lung. Coupled with the increased permeability due to the underlying disease being treated (e.g. ARDS), or the increased permeability caused by overdistension, mechanical ventilation could lead to translocation of mediators, bacteria or endotoxin into the systemic circulation. This in turn could cause end-organ dysfunction distal to the lung (e.g. kidneys) and lead to multi-organ failure7. This mechanism could explain the fact that most patients with ARDS who die, do so not because of hypoxemia but because of multi-organ failure.

To mitigate VILI Hickling and colleagues used a very intriguing strategy in treating their ARDS patients. They realized that patients that with ARDS usually die of multiple system organ failure, not hypoxemia; and that respiratory acidosis is very well tolerated if the patient is not hypoxemic. As such, they prioritized a ventilatory strategy in which limiting lung stretch (to limit VILI) was more important than the maintenance of normal blood gases. Their strategy, which they called permissive hypercapnia, demonstrated a decrease in mortality compared to a historical control group. The mean value of PCO$_2$ was 66 mmHg, with one patient reaching a PCO$_2$ of 158 mmHg; the lowest pH was 6.79. This strategy was similar to a strategy called controlled hyperventilation which was used successfully to treat patients with status asthmaticus; essentially: less ventilation leads to less iatrogenesis.
A number of years later, a landmark article published by the ARDS Network definitely demonstrated the beneficial effects of ventilation with low tidal volumes in patients with ARDS. They compared a strategy using low tidal volumes (6 ml/kg predicted body weight (PBW)) to higher tidal volumes (12 ml/kg PBW). Ventilation with low tidal volumes resulted in a 9% absolute decrease in mortality and increased the number of ventilator-free days. Some clinicians and investigators were relatively slow to accept these findings, but subsequent trials and a meta-analysis convincingly confirmed the reduction in mortality by using low tidal volumes in patients with ARDS. Currently, lung-protective ventilation with low tidal volumes is considered standard of care for patients with ARDS.

This study was followed by other randomized controlled clinical trials (RCTs) addressing various approaches for minimizing VILI including use of higher PEEP levels, prone position, and early, short-term neuromuscular blockade. Lung protective strategies are currently the standard of care for patients with ARDS.

There is also increasing evidence that these strategies are also important in ventilating patients who do not have ARDS. Recent evidence has demonstrated that the use of lung protective strategies can improve post-operative outcomes in patients undergoing major abdominal procedures, can prevent patients with normal lungs being ventilated in the ICU from developing ARDS, and can lead to an increase in the number of usable lungs from brain dead patients for subsequent lung transplantation. There are also ongoing studies examining whether VILI can be completely abrogated by the use of extra-corporeal lung support to decrease the intensity of mechanical ventilation or to even completely abolish it by using full support with ECMO.

In summary, this change in philosophy from focusing solely on the maintenance of normal blood gases to a focus on mitigating lung injury while maintaining "adequate" gas exchange has dramatically changed the way patients are being ventilated world-wide. It is also in synch with other evidence that "more may be less" (e.g. transfusions, anti-arrhythmia therapies) as we care for our sickest patient.

References