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EDITORIAL

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Does high tidal volume generate ALI/ARDS in healthy lungs?

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In *Intensive Care Medicine* Gajic and coworkers [1] now report that use for the first 48 h after ICU admission of high tidal volumes (>700 ml) and high peak inspiratory pressures (>30 cmH_2O) is associated with the development of the criteria for acute respiratory distress syndrome (ARDS) in patients requiring mechanical ventilation for surgery, aspiration, sepsis, pneumonia and trauma but who did not have ARDS. Do these results support the concept that stretch due to mechanical ventilation may cause ventilator-induced lung injury (VILI) in healthy lung [2]?

Mechanical ventilation is the main supportive therapy to reestablish sufficient oxygen supply to peripheral organs in all kinds of acute respiratory failure. It was recognized early that, apart from alveolar disruption, mechanical ventilation can increase alveolar-capillary permeability through the overdistension of the lung (volutrauma) and/or worsening lung injury through the tidal recruitment-derecruitment of the collapsed alveoli (atelectrauma) and lead to even more subtle injury manifested by the activation of the inflammatory process (biotrauma) [2].

The theoretical basis of VILI relies on the seminal study of Mead and coworkers [3] who examined the intrapulmonary distribution of pressure in a lung model that included normal and collapsed alveoli. In such model, tidal inflation caused (a) part of the alveoli continuously accessible to ventilation to be hyperinflated and (b) part of the collapsed alveoli to be continuously recruited and derecruited. Under these circumstances when tidal inflation generated an airway opening pressure of 30 cmH_2O, in the area encompassed between the hyperinflated and the normal alveoli and between the continuously recruited-derecruited alveoli and the normally expanded regions, the interstitial pressure was amplified to 140 cmH_2O [3]. This local amplification of pressure may generate mechanical distortion through two mechanisms: shear stress and stress failure [4].

Shear stress is a form of mechanical stress generated when air move across a cell surface, thereby generating a force parallel to the membrane that induces a tangential distortion of the cell. In damaged lungs the development of shear stress is related to the cyclic opening and closing of small airways induced by recruitment-derecruitment of alveolar units. Diseased lungs with a heterogeneous distribution of lesions may be subjected to much greater regional stress than homogeneous lungs. The occlusion of small airways by exudate or apposition of their walls requires high airway pressure to restore airway opening, resulting in shear stress and damage, particularly if the cycle is continuously repeated [4, 5].

Stress failure depends on the development of excessive wall stress, defined as the ratio of alveolar wall tension to thickness. The limited strength of the alveolar-capillary barrier may explain such mechanism of mechanical stress. It is known that high airway pressure between the alveolus and the vascular bed during positive pressure ventilation causes the passage of air across the epithelial surface, along the bronchovascular sheath, and then into the interstitial tissues. The endothelium, so close to the epithelial surface, is subject to stress failure determined by forces

derived from both transpulmonary and intravascular pressures. The local or regional stress induced by lung inflation may increase microvascular transmural pressures with disruption of capillaries and change the alveolar-capillary barrier. The forces generated by mechanical ventilation may therefore interact with those due to pulmonary vascular perfusion to increase lung injury [4, 6].

These data therefore led to the concept that (a) all the pathophysiological characteristics of ARDS (ventilation-perfusion mismatch and reduced compliance, lung edema, atelectasis, pulmonary inflammation) may be worsened by inappropriate ventilator settings because of the nonhomogeneous distribution of normal lung regions mixed with consolidated, atelectatic regions and regions that can be recruited/de-recruited depending on the particular ventilatory strategy used [7]; (b) normal, homogeneous lungs should not be affected by ventilator settings otherwise injurious for nonhomogeneous lung [4, 8].

Lungs of patients recovering from abdominal surgery are asymmetric along the vertical axis with relatively normal regions located in the nondependent zones, areas of partially collapsed lung and/or alveolar filling located in the middle zones, and area of pulmonary consolidation located in the most dependent regions [9]. Also in these patients mechanical ventilation may hence theoretically induce shear stress and stress failure because of recruitment-derecruitment of atelectatic alveoli and hyperinflation of normal alveoli [4]. However, Wrigge and coworkers [10, 11] found that in patients after minor surgical procedures mechanical ventilation with tidal volumes of 0.8–1.2 l induced no relevant increase in inflammatory mediators.

Similarly to patients following abdominal surgery, the lungs of patients after cardiopulmonary bypass (CPB) for cardiac surgery are asymmetric along the vertical axis with normal regions, areas of partially collapsed lung and/or alveolar filling, and area of pulmonary consolidation located in the nondependent, intermediate, and most dependent regions, respectively [12]. In a recent study in patients requiring CPB for cardiac surgery we found pulmonary and plasmatic concentration of inflammatory mediators to be increase after 6 h of mechanical ventilation only in those patients ventilated with tidal volumes of 10–12 ml/kg (measured body weight) and 2–3 cmH_2O of PEEP, and decreased after 6 h of mechanical ventilation with a tidal volumes of 8 ml/kg (measured body weight) and 10 cmH_2O of PEEP [13].

Two conditions may therefore be required for stress due to mechanical ventilation to induce a relevant inflammatory stimulus: (a) the mechanical conditions determining the activation of mechanical forces such as shear stress and stress failure; (b) the presence of a primary inflammatory stimulus represented by the underlying causes of ARDS [14], by CPB [13] or other ischemia-reperfusion conditions such as lung transplant [15]. Preliminary data from Wrigge and coworkers [16] indicate that after cardiac surgery, ventilation with low tidal volumes decrease pulmonary inflammatory mediators particularly in patients in whom CPB induced a more relevant increase in pulmonary concentration of inflammatory mediators.

Did the lungs of patients included in the Gajic et al. study have both the mechanical conditions and a primary inflammatory stimulus theoretically required to develop VILI? The PaO_2/FIO_2 ratio was lower and the incidence of pneumonia greater in the group that 48 h after ICU admission developed ARDS than in the group that did not develop ARDS. Moreover, acute respiratory failure due to surgery, aspiration, sepsis, pneumonia, and trauma are associated with an overexpression of the inflammatory response [17]. Data from the Gajic et al. study may therefore confirm that mechanical stretch can activate VILI in lungs already injured and inflamed although the observational nature of the study does not provide definitive answers. However, more important than the contribution to the understanding of the basic mechanisms involved with VILI, their study confirms that the use of high tidal volumes is associated with a serious and severe worsening of the clinical prognosis of mechanically ventilated patients. Until future studies become available, clinicians should be extremely cautious in using ventilator settings that lead to plateau pressures higher than 30 cmH_2O in patients without ARDS [1, 18], and the National Institutes of Health protective strategy must be the gold standard ventilatory treatments for patients with ARDS [19, 20].

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