Transpulmonary pressure: A more pathophysiological open lung approach?*

The positive end-expiratory pressure (PEEP) is an essential tool in the ventilator management of acute lung injury/adult respiratory distress syndrome (ALI/ARDS). Although the PEEP improves gas exchange and reduces the intrapulmonary shunt and the ventilator-induced lung injury, its setting is still a matter of controversy in ALI/ARDS patients. Several clinical trials comparing different strategies to select PEEP showed no benefit in mortality. Among them, the ExPress trial proposed to progressively rise the PEEP with a constant tidal volume of 6 mL/kg of predicted body weight to reach an inspiratory airway pressure between 28 cm H₂O and 30 cm H₂O, which was proposed by the authors as a recommended value to avoid lung hyperdistention. Although in clinical practice the airway pressure is assumed to be a surrogate for the transpulmonary pressure, this is highly questionable due to the extreme variability of the chest wall elastance.

In static condition:

\[ P_{aw} = P_{pl} + P_L \]

where \( P_{aw} \) is the airway pressure, \( P_{pl} \) is the pleural pressure, and \( P_L \) is the transpulmonary pressure.

Consequently, in ALI/ARDS patients without considering the lung and chest wall elastance, it is not possible to estimate the transpulmonary pressure and consequently to assess the possible risks of lung overdistention or collapse. As an example, a “safe” airway plateau pressure might result in lung collapse when the chest wall elastance is increased.

In this issue of Critical Care Medicine, Staffieri et al (9) applied the Express protocol in a large animal model of ARDS and reversible chest/abdomen restriction (i.e., which increased the chest wall elastance) to underline possible differences between the airway and transpulmonary pressure. In fact, the authors hypothesized that in the presence of chest/abdomen restriction, the airway pressure increased and falsely reflected the lung distention, thus the PEEP set according with the Express protocol based on airway pressure measurement would be inadequate low and would result in alveolar collapse. A target of end-inspiratory transpulmonary pressure of 26 cm H₂O was chosen, based on the upper limit of airway pressure from the ExPress trial considering a quite normal chest wall elastance of ALI/ARDS patients. The authors found that during chest/abdomen restriction with a PEEP set according with Express protocol without taking into account the transpulmonary pressure, the level of PEEP, the amount of not aerated tissue (computed by lung computed tomography scan at end expiration), and oxygenation were significantly higher and lower compared to normal chest wall conditions. On the contrary, during chest/abdomen restriction and PEEP based on the transpulmonary approach, the level of PEEP and oxygenation were significantly higher and the amount of not aerated tissue lower compared to the Express protocol. In addition, by maintaining the same end-inspiratory transpulmonary pressure in presence or in absence of chest/abdomen restriction, the oxygenation and the amount of nonaerated and hyper-inflated tissue were similar between the two groups. Contrary to lung computed tomography scan findings, the stress index was significantly lower in the chest/abdomen restriction with the low PEEP compared with high PEEP. Despite the well-known limitations of the esophageal pressure as surrogate of pleural pressure (10, 11), this study clearly shows that in presence of a chest/abdomen restriction, the use of end-inspiratory transpulmonary pressure instead of airway pressure caused the setting of higher PEEP levels with the same amount of not aerated lung tissue. This study also confirms previous findings in which the stress index computed on the airway pressure tracing was unable to follow lung recruitment in the presence of an altered chest wall elastance (12, 13). Unfortunately, this study did not compare different levels of end-inspiratory transpulmonary pressure (i.e., higher or lower lung distending force) or delta transpulmonary pressure on the ventilator-induced lung injury. However, an end-inspiratory transpulmonary pressure not higher than 26 cm H₂O, reaching by increasing the PEEP, maintaining constant the tidal volume, did not clinically increase the overinflated tissue.

Similarly, a quite recent study demonstrated that rising PEEP to reach an end-inspiratory transpulmonary pressure of 27 cm H₂O improved the oxygenation and allowed to continue conventional mechanical ventilation instead of extracorporeal membrane oxygenation in patients with influenza H1N1 (8). Conversely, Protti et al (7) showed in healthy pigs ventilated with no PEEP that a transpulmonary pressure of 13 cm H₂O compared with 8 cm H₂O significantly induced edema formation. It must be noted, however, that in healthy pigs the specific elastance is about half compared to human being. Therefore, 13 cm H₂O of transpulmonary pressure in pigs should be roughly equivalent to 26 cm H₂O in human.

However, the chest/abdomen restriction by increasing the pleural pressure not only decreases the ability of the airway pressure to reflect the end-inspiratory transpulmonary pressure but also reduces the end-expiratory transpulmonary pressure promoting the alveolar collapse for the same PEEP level. In this line, Loring et al (14) showed in an animal model of ALI that a thoracoabdominal constriction significantly increased the mediator release and edema formation, which could be reduced by additional PEEP to reach...
Antisense inhibition of phospholipase A2: A new approach for already tested therapeutic targets for the treatment of sepsis*

Sepsis is generally defined as a life-threatening illness due to the body over-reaction to an infection. During sepsis the immune system goes into overdrive, leading to a series of reactions resulting in a "stormy" inflammatory reaction that escape host control accompanied with blood clotting in the body. Multiorgan failure, such as acute respiratory distress syndrome, belongs to the complications of sepsis. Numerous inflammatory mediators have been reported to play a key role in the pathogenic process of sepsis (1). This includes cytokines and lipid mediators such as arachidonic acid metabolites and platelet-activating factor produced by phospholipases A2 (PLA2s)-catalyzed reaction (2). In mammals, PLA2s hydrolyze membrane phospholipids of host cells and are classified into four major groups: 1) secreted PLA2 (sPLA2), 2) cytosolic PLA2 (cPLA2), 3) Ca2+-independent intracellular PLA2, and 4) acidic Ca2+-independent PLA2. Following its release by PLA2s, arachidonic acid is metabolized by a variety of enzymes, including cyclooxygenases and lipoxygenases leading to the production of eicosanoids involved in the modulation of inflammation.

Near 20%–35% of patients with severe sepsis and 40%–60% of patients with septic shock dies within 30 days. The clinical and economical burden due to sepsis is very high, and although treatment modalities have improved the patient outcome (3), the mortality rate remains unacceptably high. Clinical trials using approaches neutralizing proinflammatory cytokines and activated protein C showed only a weak efficacy (2%–4%) (4). Subsequent studies showed increased levels of sPLA2-IIA (a particular isoform of sPLA2), platelet-activating factor, and cyclooxygenase metabolites in plasma of patients with severe sepsis that were inversely correlated with survival. However, clinical trials targeting these molecules did not improve survival at 30 days in sepsis patients (5–7). These disappointing results and others led to the arrest of clinical trials and to the statement that “For sepsis, the drugs don’t work” (8).

The lack of efficacy of these trials can be explained by the fact that the pharmacological agents are directed to a single PLA2, a single subsequent pathway, or a single mediator. Using a rat model of sepsis, Liu et al (9) have examined whether simultaneous inhibition of cPLA2 and sPLA2-IIA expressions benefits the eventual outcome of the disease. The authors

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*See also p. 2132.

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