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EDITORIAL

Ventilation-induced lung injury exists in spontaneously breathing patients with acute respiratory failure: We are not sure

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The existence of ventilation/ventilator-induced lung injury (VILI) during spontaneous breathing cannot be denied, as it has been shown experimentally [1] and, at least, suspected in some clinical circumstances [2]. Therefore it is nonsense to be pro or con towards the facts. One, however, may be pro or con the opinion that spontaneous breathing, either with or without mechanical ventilation, favors a lower occurrence of ventilator-induced lung injury (VILI) compared to mechanical ventilation alone. Before discussing this problem, it is convenient to precisely define the VILI and the conditions for its development.

We define here VILI as the mechanical lesions which develop in the lung when an "excessive" mechanical power is transferred to the lung parenchyma [3]. We will not therefore consider here other situations such as pneumonia or deterioration of hemodynamic-related lung edema, which may be associated with mechanical ventilation or spontaneous breathing, but are not necessarily linked to the mechanical forces. The mechanical lesions develop in the interstitial space as microfractures of the matrix [4] or of the capillary walls [5, 6]. In fact, when the polymers composing the extracellular matrix are overstretched, some of the molecular bonds will break, generating polymers of lower molecular weight, which in turn, via toll receptors, may activate the inflammatory cascade [7]. The microfractures may be considered analogous to those of metals undergoing repeated cycles of high stress and strain. They require several cycles (i.e., time) to develop, but when they occur the lesions spread rapidly throughout the material [8].

For VILI to occur, however, two conditions are required. The first is ventilator-related and is the mechanical power. This is composed of the product of tidal volume, driving pressure, and respiratory rate, to which the contribution of the positive end-expiratory pressure must be added [9]. The second condition for VILI development is lung-related and is primarily the extent of the inflammatory edema. The greater it is, the lower the ventilatable lung size is and the greater the lung parenchyma inhomogeneity becomes. The mechanical power, the lung size, and the extent of inhomogeneity obviously interact in the generation of VILI.

In this context, we may discuss the main differences (and the consequences on VILI) between spontaneous and mechanical ventilation.

The main differences are related to:

1. *Intrathoracic pressure* It is negative and/or decreases during the inspiration in spontaneous breathing, while it is positive and/or increases during the inspiration in mechanical ventilation.
2. *Diaphragm dynamics* During spontaneous efforts the posterior portion of the diaphragm moves caudally to a greater extent than the anterior-ventral portion, whereas this does not occur during passive inflation.
3. *Power source* The energy is provided by the respiratory muscles during spontaneous breathing and by electrical power during mechanical ventilation (note that the greater the contribution of the respiratory muscles is, the greater the minute ventilation requirements due to increased oxygen consumption will be).

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We may then discuss if and how these differences may make VILI more probable in spontaneous breathing than in mechanical ventilation or vice versa.

- *Intrathoracic pressure* Its negativity or positivity conditions the hemodynamics, favoring the venous return during spontaneous breathing and disfavoring it during mechanical ventilation. In isolated lungs the filling status of the pulmonary capillaries has been described as a possible cofactor for VILI [10]; however, clinical data supporting this hypothesis are scanty. Excessive negative intrathoracic pressure implies an increased negativity of the interstitial pressure, favoring the formation of edema, as described near 80 years ago by Barach [11], but this phenomenon cannot be considered VILI as we defined it above. Therefore the differences in behavior of the intrathoracic pressures, during spontaneous breathing and mechanical ventilation, may be hardly considered a major cause of VILI, although a possible contribution to VILI cannot be excluded (note that here we are referring only to the intrathoracic pressure and not to the transpulmonary pressure, see below).
- *Diaphragm dynamics* During spontaneous breathing, the posterior portion of the diaphragm moves caudally to a greater extent than the anterior-ventral portion, thus preventing/correcting the atelectasis at the lung bases [12]. These are actually frequent in the acute respiratory distress syndrome (ARDS), because of the weight of the lungs [13] and heart [14]. During mechanical ventilation, in contrast, the ventilation is disproportionately distributed in the non-dependent lung regions. In fact, the displacement of the diaphragm is greater in the non-dependent portion, where the abdominal pressure is least. These differences in diaphragm dynamics between spontaneous and mechanical breathing, however, tend to decrease when PEEP is applied or prone position is used. Indeed, the diaphragm dynamics are not likely, per se, to account for different incidences of VILI during spontaneous or mechanical ventilation.
- *Power source* While the mechanical power during passive inflation is provided by an external source of energy, during spontaneous breathing it is provided by the respiratory muscles. Actually, what causes VILI is the mechanical power applied to the lungs, which generates the transpulmonary pressure (ΔP_L, difference between the airways and the pleural pressure). The following equation shows that (in static conditions) the ΔP_L, i.e., the distending force of the lung, is a function either of the pressure applied by the ventilator (ΔP_{aw}) or that generated by the muscles (ΔP_{musc}), multiplied by the ratio between the elastance of the lung (E_L) and the elastance of the respiratory system (E_{tot}, lung plus chest wall):

$$\Delta P_L = (\Delta P_{aw} + \Delta P_{musc}) \cdot \frac{E_L}{E_{tot}}$$

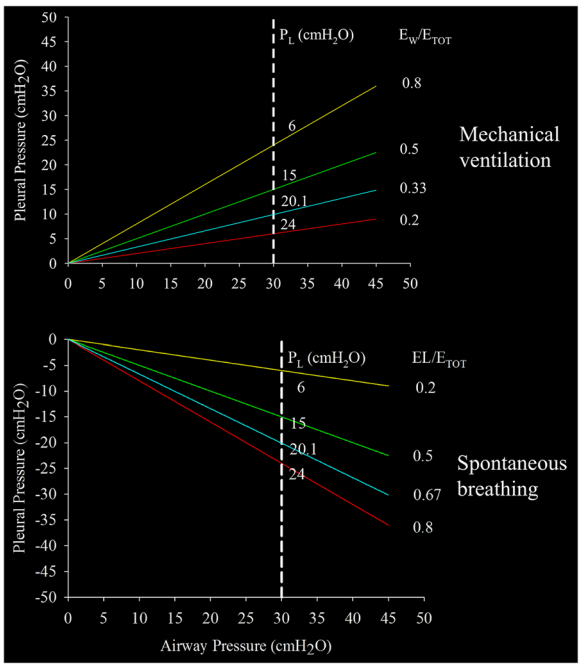

Fig. 1 Pleural pressure as a function of airway pressure in mechanically ventilated (*upper diagram*) and spontaneously breathing patients (*lower diagram*). As shown, at 30 cmH_2O airway pressure, the transpulmonary pressure (P_L) may range in both cases from 6 to 24 cmH_2O, according to the elastances ratios (E_L is the lung elastance, E_w is the chest-wall elastance, E_{tot} is total elastance of the respiratory system)

Therefore, the amount of VILI will be the same (in a lung characterized by a given E_L/E_{tot} ratio) if a harmful transpulmonary pressure is generated either by the muscles (in spontaneous breathing $\Delta P_{aw} = 0$) or by the ventilator (in mechanical breathing $\Delta P_{musc} = 0$). The lungs ignore if they are moved or overdistended by the muscles or the ventilator: VILI depends on the level of power applied, not on its source. The above equation emphasizes the importance of the E_L/E_{tot} ratio. In fact it determines the fraction of the applied pressure, either from ventilator or from respiratory muscles, which generates the transpulmonary pressure. In ARDS the E_L/E_{tot} ratio may vary from 0.2 to 0.8, with the effects shown in Fig. 1.

As an example, the same "harmful" transpulmonary pressure of 25 cmH_2O, close to the one required to reach the total lung capacity [15], may be equally reached during totally spontaneous breathing (as we observed in ARDS

patients during ECMO, unpublished data), by mixed spontaneous and mechanical breathing (as during non-invasive ventilation) or by total mechanical ventilation.

In conclusion, VILI may occur with equal probability in spontaneous or mechanical breathing if both modes generate the same mechanical power. Several factors other than the ones discussed above (such as hemodynamics, ventilation level, ventilatory control, protective reflexes, actual interstitial pressures during the inflation process, distribution of transpulmonary pressures) may contribute to VILI during spontaneous breathing and mechanical ventilation. However, in this editorial we chose to use Occam's razor, for which "Among competing hypotheses, the one with the fewest assumptions should be selected".

Compliance with ethical standards

Conflicts of interest
The author states that there is no conflict of interest.

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