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UNDERSTANDING THE DISEASE

Ventilator induced lung injury: a case for a larger umbrella?

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Mechanical ventilation and VILI

Ventilator-induced lung injury (VILI) is a general term indicating the structural and physiological lung alterations caused by mechanical ventilation (MV). Given that MV is only a supportive treatment, the best MV settings are those providing sufficient gas exchange without generating additional injury. Therefore, VILI detection allows to discriminate between an "innocent" and a "harmful" MV.

Conceptual and mechanistic evolution of ventilator-induced lung injury

Barotrauma

This was the first described injury associated with MV in acute respiratory distress syndrome (ARDS). The mechanism of these injuries was elucidated by Macklin et al. [1], who found that alveolar rupture leads to a gas escaping along the pulmonary vascular sheaths toward the mediastinum with consequent pneumomediastinum, subcutaneous emphysema, and pneumothorax.

Volutrauma

Dreyfuss et al. [2] first recognized that the main determinant of VILI was an excessive strain (i.e., the change in volume compared to the initial volume). The relationship between strain and pulmonary edema was investigated by measuring the lung capillary permeability (^{125}I-labeled albumin). The concepts of barotrauma and volutrauma led to the development of lung protective ventilation.

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Atelectrauma

The relationship between atelectasis and VILI was demonstrated by Tremblay et al. [3], with ex vivo experiments showing that atelectasis increased inflammation. This work was based on models developed by Mead et al. [4] that estimated that the pressure developed at the interface between consolidated and open pulmonary units was 4–5 times higher than the applied airway pressure. The attempt to prevent atelectrauma led to the open lung approach.

Biotrauma

This term underlines the relationship between mechanical stress and strain and the generation of a local and systemic inflammatory response with an increase in cytokines.

Ergotrauma

This term denotes the relationship between mechanical energy delivered to the respiratory system at each breath and VILI. Energy (Joules) combines tidal volume, driving pressure, and end expiratory pressure (PEEP). Mechanical energy multiplied by the respiratory rate gives mechanical power—MP (Joules/min) [5] which is associated with worse outcome.

VILI pathogenesis

In healthy lungs

In Fig. 1, we summarize two, not-mutually exclusive, pathways resulting from ventilation with injurious MP. The first leads to a structural modification of the lung parenchyma (alveolar ruptures and extracellular matrix fragmentation), with secondary inflammation [6], increased capillary permeability and edema, increased lung weight and formation of compression atelectasis [7]. The second results from an increase in pleural pressure and hemodynamic depressions which leads to fluid

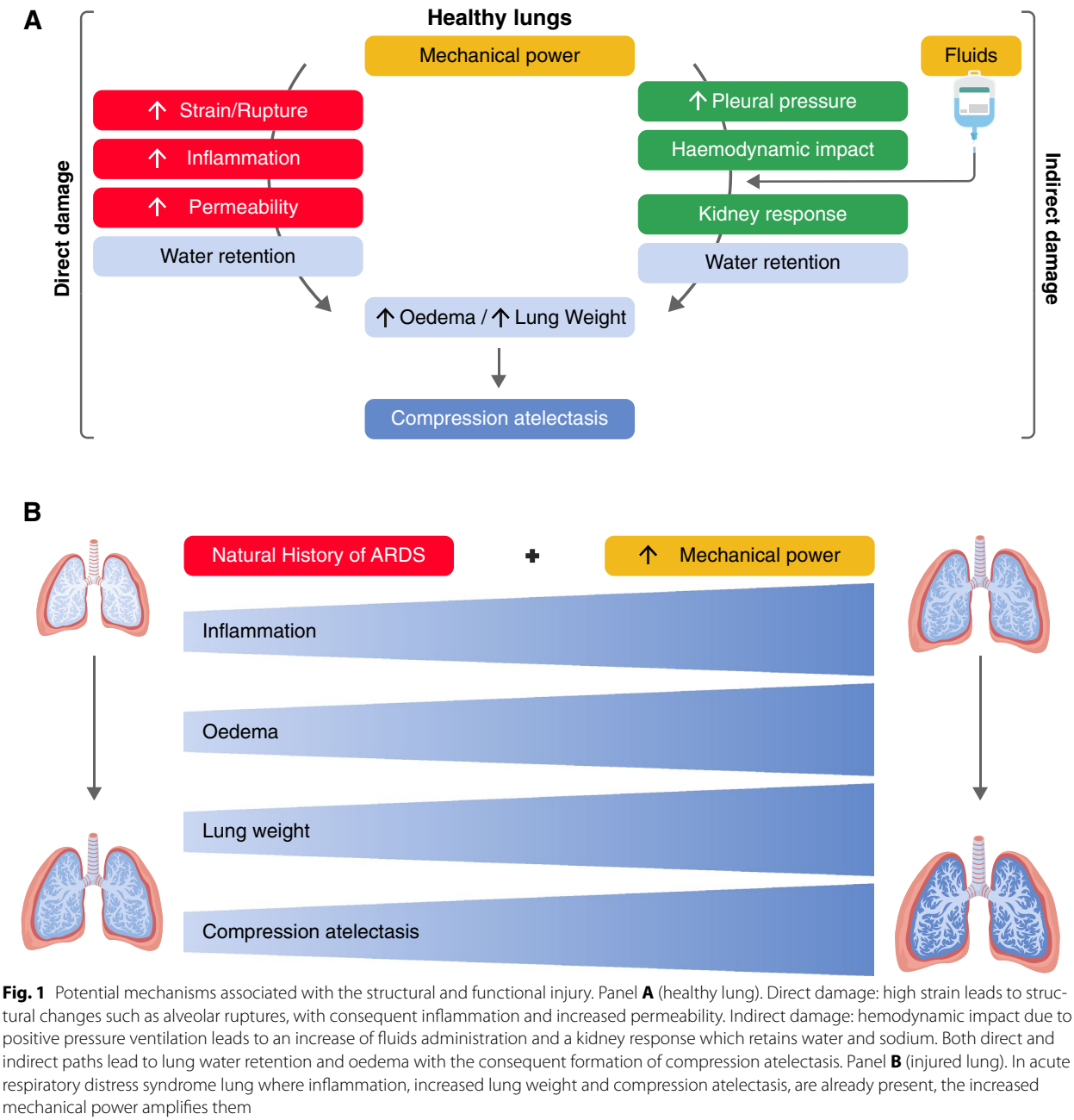

Fig. 1 Potential mechanisms associated with the structural and functional injury. Panel **A** (healthy lung). Direct damage: high strain leads to structural changes such as alveolar ruptures, with consequent inflammation and increased permeability. Indirect damage: hemodynamic impact due to positive pressure ventilation leads to an increase of fluids administration and a kidney response which retains water and sodium. Both direct and indirect paths lead to lung water retention and oedema with the consequent formation of compression atelectasis. Panel **B** (injured lung). In acute respiratory distress syndrome lung where inflammation, increased lung weight and compression atelectasis, are already present, the increased mechanical power amplifies them

administration, water retention, positive fluid balance, increased lung weight and compression atelectasis.

In injured lungs

Inflammatory edema and pulmonary hypertension characterize ARDS. VILI induces similar alterations, making impossible to discriminate between the natural history of ARDS and the contribution of harmful MV. A possible simplified schema is presented in Fig. 1, Panel B. As shown, VILI enhances the pathological features of ARDS and adds the structural changes to the lung parenchyma due to the ventilation of smaller and inhomogeneous lungs (baby lung).

VILI assessment

As the gold standard to estimate VILI, i.e., emphysema-like histology lesions, cannot be directly assessed *in vivo*, we attempt to identify variables associated with

the structural injury and with their physiological consequences (Fig. 1).

Strain/rupture

The physiological variables best associated with lung structural changes are: (2) the specific elastance (E_s) (i.e., elastance per liter of volume), which increases when emphysema-like lesions occur [8]. Unfortunately, its measurement is rare as technically difficult to obtain; (2) the physiological dead space, which is associated with lung structural changes and outcome [9].

Inflammation/permeability

The increase in inflammatory cytokines during high volume ventilation was considered a sign of VILI in a seminal paper by Ranieri et al. [10]. The specific markers of capillary permeability are lacking, and the increased edema may depend on several factors other than permeability.

Water retention

Water retention and edema formation, which may be assessed by fluid balance, are the consequence of hemodynamic and neuro-hormonal changes that regulate water and electrolyte homeostasis. These alterations can be estimated by measuring urinary electrolytes and sodium/potassium ratio.

Edema and lung weight

The available imaging techniques (e.g., computed tomography (CT), lung ultrasound and electrical impedance tomography), although with different physical basis, estimate the same phenomenon, i.e., the ratio between gas and tissue volume—where tissue includes edema. Extravascular lung water measurement is another possibility to quantify lung edema. An indirect assessment of the gas content (decreased during the edema state) is the measurement of respiratory system elastance, whose increase is strictly associated with decrease of the "baby lung" size.

Compression atelectasis

All the techniques used to assess lung recruitability (imaging, respiratory mechanics, and gas exchange) estimate the amount of lung atelectasis.

Hemodynamic and its consequences

The hemodynamic changes are deeply interwoven with MV as the increase in pleural pressure is associated both with pulmonary hypertension and decreased cardiac output. With fluid therapy, the consequences are similar as observed with VILI-induced structural lung changes, i.e., water retention, edema and atelectasis [11].

Clinical approach to VILI

The fundamental mechanisms driving VILI can be identified experimentally in healthy animals, where all the alterations on lung structure and function can be exclusively attributed to MV. Experimental studies demonstrated that excessive tidal volume, driving pressure, respiratory rate, and PEEP cause VILI. In clinical settings, alterations induced by VILI are indistinguishable from those resulting from the primary pathology. Therefore, in ARDS trials, the attributable mortality of VILI is inferred by difference in outcome between groups. This procedure allowed to confirm that higher tidal volume [12] and driving pressure [13], as well as higher PEEP/recruitment [14] and high respiratory rate [15] may all produce a worse outcome.

The presence of VILI can only be suspected/inferred based on deterioration of physiological variables associated with it. The question is whether the alterations due to the hemodynamic, summarized in Fig. 1 as indirect lung injury, may be classified under the "VILI umbrella". We believe that it is prudent to include, within the VILI concept, all the direct and indirect pathological changes occurring during MV. The challenge is then to identify a mechanical threshold for VILI. Indeed, it is likely that in some patients, VILI is unavoidable due to the dimension of the "baby lung". The impossibility of "safe ventilation" is the rationale for resorting to extracorporeal support.

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