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Understanding lung protection

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During the past two decades lung protection has emerged as a central tenet in the management of patients with respiratory failure. While the biophysical determinants of so-called ventilator-induced lung injury (VILI) are principally understood, translating this knowledge into specific "safe" ventilator settings remains controversial. Although a landmark study by the ARDS Network unequivocally demonstrated harm caused by mechanical ventilation with large tidal volumes, there is no consensus on how to best tailor ventilator mode and settings to patient-specific information about respiratory mechanics, gas exchange, and cardiovascular function [1]. This uncertainty manifests in diverging opinions about optimal recruitment strategies and positive end-expiratory pressure (PEEP) management; about the relative merits of adjusting ventilator settings to driving pressure as opposed to tidal volume and end-inflation plateau pressure (Pplat); in controversies about the VILI risk in spontaneously breathing and/or partially assisted patients; and in a continued search for more efficacious lung protective modes of respiratory support [2, 3]. High frequency oscillatory ventilation (HFOV) was to be such a mode by virtue of supporting gas exchange while keeping the lungs' tidal oscillations at low and presumably safe levels. This hope was not borne out in two recently published clinical trials, causing Dreyfuss and colleagues in this issue of *Intensive Care Medicine* to argue that in spite of low tidal volumes the large end-inspiratory lung volumes and parenchymal stresses associated with HFOV may in fact cause VILI [4–6].

To make sense of the complex interactions between ventilator output and the lungs' response it is important to remember that the physical properties of lung parenchyma differ from those of an ideal spring. The tension in an ideal spring is entirely determined by its length and independent of the rate and magnitude of the preceding length change. In contrast the tension in an alveolar wall or lung tissue strip varies not only as a function of its final length but is also influenced by the rate and magnitude of the preceding deformation. This property is a manifestation of parenchymal plasticity and reflects the deformation-induced molecular rearrangements of surfactant proteins and lipids and of the stress-bearing biopolymer networks of cells and connective tissue [7].

Lung parenchymal plasticity implies that VILI risk is unlikely to be determined by a single variable. For certain, repeatedly stretching the lungs to volumes in excess of their physiologic capacity risks damage, but it also matters how peak lung volume is reached, suggesting that tidal volume, inspiratory flow, and respiratory rate all have a modifying influence on injury risk. Expert opinion holds that keeping Pplat below 30 cm H_2O minimizes the risk of lung injury by overdistension. While adherence to this recommendation will serve this objective in most instances, it does risk atelectasis from lung compression in recumbent patients with large abdominal loads [8]. The latter raises concerns about a different injury mechanism, namely epithelial wounding on account of interfacial stress [9]. This mechanism is often referred to as "atelectrauma" or "opening and collapse injury" and

motivates proponents of aggressive lung recruitment and PEEP management strategies [10].

Since the potentially harmful HFOV mode represents an aggressive lung recruitment strategy, one could conclude that in patients with adult respiratory distress syndrome (ARDS) the risk of injury by overdistension outweighs the dangers of atelectrauma. Be this as it may, there are additional interpretations and injury mechanisms that warrant consideration. The microvasculature of injured lungs contains thrombi and is exposed to vasoactive mediators accounting for increased pulmonary vascular resistance. In that context aggressive recruitment strategies can cause hypotension and obstructive shock. It is often difficult to define, interpret, and manipulate the cardiovascular consequences of lung protective interventions in small animal models, which have informed many of the prevailing hypotheses about ventilator management and VILI pathogenesis. This is important because interventions that effect a decrease in pulmonary blood volume and flow may give rise to a favorable histologic appearance of the lungs, with fewer perivascular hemorrhagic lesions, fibrin deposits, and less edema. For example, Webb and Tierney drew attention to the lung protective effects of PEEP, by demonstrating that a PEEP-mediated reduction in driving pressure prevented hemorrhagic pulmonary edema in rats ventilated to a peak pressure of 40 cm H_2O [11]. This was a seminal observation that inspired many subsequent investigations into the pathogenesis of VILI, yet to this data leaves fundamental questions about mechanisms including the confounding influence of pulmonary perfusion on histologic injury markers unanswered [12].

Present ventilator management guidelines focus on Pplat, tidal volume, and driving pressure, but are relatively non-committal on rate. The focus on tidal volume and driving pressure is appropriate because both are determinants of tissue deformation and associated changes in parenchymal stress. In ex vivo mechanically ventilated and perfused lungs it has been shown that frequency has a modifying influence on the physiologic and morphologic manifestations of injury [13]. However, it is unclear whether these observations can be extrapolated to frequencies encountered during HFOV. Oscillatory mechanics have been measured in lung cells over a wide range of frequencies and have consistently shown a monotonic increase in stiffness as a weak power function of rate [14]. These observations suggest that at frequencies typically encountered during HFOV, the stress at molecular junctions between epithelial cells, endothelial cells, and their respective adhesion sites with the capillary basement membrane could reach failure levels. This hypothesis, if accepted, implies that frequency reduces the volume threshold at which the lungs' barrier properties become impaired [15].

The complexity of biophysical lung injury mechanisms argues for a nuanced approach to lung protective mechanical ventilation (Table 1). While prevailing guidelines for the ventilator management of patients with ARDS are undoubtedly shaped by concerns for VILI, key elements are based on assumptions that may not hold across the spectrum of disease. Tidal volume guidelines

Table 1 Common ventilator management guidelines for patients with ARDS

Common ventilator setting guidelines	Rationale	Caution
Tidal volume (VT) = 6 ml/kg predicted body weight	Actual body weight bears no relationship to lung size	Predicted body weight (PBW) scales with the size of the healthy uninjured lung. Since in severe ARDS a large number of alveoli are flooded and/or collapsed scaling VT to PBW as opposed to measured lung capacity may not prevent VILI
Keep end-inflation hold/plateau pressure (Pplat) below 30 cm H_2O	Keeps maximal transpulmonary pressure (i.e., maximal parenchymal stress) in a safe range	Recommendation assumes normal chest wall mechanics and respiratory muscle relaxation at end-inspiration. Therefore, it does not guard against VILI from overdistention in patients with persistent diaphragm activity, particularly when associated with breath stacking. It may also prevent optimal PEEP/VT adjustments in recumbent patients with increased abdominal pressure
Perform a recruitment maneuver and titrate PEEP to maintain recruitment gains	Minimize O_2 supplementation requirements while preventing atelectrauma	Guard against VILI from overdistension by adhering to Pplat guidelines and by keeping driving pressure from rising during PEEP titrations. Recommendation requires a careful assessment of the hemodynamic response with particular attention to right heart function
Keep driving pressure below 20 cm H_2O	Avoid overdistension	Recommendation assumes normal chest wall mechanics and surface tension in "open" i.e., recruited alveoli. It remains controversial/unproven that a "safe" driving pressure is a license for exceeding conventional VT and Pplat safety guidelines

do not take the number of recruitable lung units, i.e., the effective size of the injured lung, into account; driving pressure and Pplat guidelines assume normal chest wall mechanics; PEEP recommendations are based on assumptions about the efficacy of lung recruitment and the relative risk of atelectrauma; respiratory rate guidelines are largely based on concerns about dead space and CO_2 elimination and are not based on concerns for harmful interactions with other VILI risk factors. These examples highlight the many remaining questions in a seemingly mature field and should challenge clinicians to consider instances when one size may not fit all.

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