CRITICAL CARE

VIEWPOINT

Beyond volutrauma in ARDS: the critical role of lung tissue deformation

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Abstract

Ventilator-induced lung injury (VILI) consists of tissue damage and a biological response resulting from the application of inappropriate mechanical forces to the lung parenchyma. The current paradigm attributes VILI to overstretching due to very high-volume ventilation (volutrauma) and cyclic changes in aeration due to very low-volume ventilation (atelectrauma); however, this model cannot explain some research findings. In the present review, we discuss the relevance of cyclic deformation of lung tissue as the main determinant of VILI. Parenchymal stability resulting from the interplay of respiratory parameters such as tidal volume, positive end-expiratory pressure or respiratory rate can explain the results of different clinical trials and experimental studies that do not fit with the classic volutrauma/ atelectrauma model. Focusing on tissue deformation could lead to new bedside monitoring and ventilatory strategies.

Introduction

Mechanical ventilation is the cornerstone of treatment for acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS). Like any other treatment, mechanical ventilation can also have adverse effects. Among these treatments, ventilator-induced lung injury (VILI) is one of the most studied. Since the first descriptions of the physical factors (pressure, volume, and so forth) involved in VILI, many mechanisms that promote lung injury – from lung mechanics to biochemical responses – have been identified [1], and ventilatory strategies aimed at reducing lung injury have been devised. The evidence for a clinical counterpart of VILI,

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which has been termed ventilator-associated lung injury, is more subtle, because the ventilatory settings are not as aggressive and the nature of lung injury in this case is always multifactorial [2]. Diverse clinical trials have studied the effects of protective ventilation strategies aimed at reducing ventilator-associated lung injury [3-13], but few studies have shown survival benefits [4,8,10].

In the current paradigm of VILI, high positive end-expiratory pressure (PEEP) should be one of the most powerful strategies to decrease VILI [14]. Recently published trials have failed to show a clear benefit for high PEEP levels in a general population of patients with ALI and ARDS [9,11,12]. The mechanisms supposedly involved in VILI should therefore be reappraised to explain the failure of high PEEP levels and to design new therapeutic approaches to ALI/ARDS. The present article reviews the current paradigm of VILI and its limitations, and discusses additional explanations that can serve as a basis for the development of new strategies.

The classic paradigm of ventilator-induced lung injury

The classic paradigm of VILI maintains that there are two main physical triggers of lung injury during ventilation: overdistension of alveolar units (volutrauma) and cyclic changes in nonaerated lung (atelectrauma). High inspiratory lung volumes or pressures can cause injury through alveolar overdistension. Although there has been some debate about the primary force that causes injury, both volume and pressure are two sides of the same coin – transpulmonary pressure. At the cellular level, stretching the lung beyond its capacity ruptures alveolar cell membranes [15], and the resulting cell death induces inflammation. Moreover, subtler injuries to the cytoskeleton or extracellular matrix trigger inflammation through intracellular signals [16].

The second mechanism of injury, cyclic changes in nonaerated lung, was deduced from the observation of lung injury during ventilation with low end-expiratory lung volume (EELV) or in the absence of PEEP. In this case, the mechanisms at the cellular level are less clear. Air bubbles flowing through a collapsed or fluid-filled airway might induce damage to the epithelium by

generating a steep pressure gradient near the air bubble front [17]. A second consequence of low EELV can be a heterogeneous lung, and Mead and colleagues showed that the forces exerted on alveolar walls or septa in the interfaces between collapsed and aerated lung tissues can be amplified, leading to cell injury [18].

Discrepancies with the model

Some observations from experimental and clinical research do not fit with the classical paradigm. The application of PEEP is almost invariably associated with a decrease in VILI in different experimental models of lung injury, such as high tidal volume (Vt) ventilation [14] or surfactant depletion [19]. When translating these models into clinical practice, a reduction in mortality has been found primarily in studies in which high PEEP is part of a greater strategy that includes low Vt [4,10]. Experimental designs combining high PEEP with low Vt make it impossible to clarify the contributions of each factor to the outcome. These clinical results are far from the sometimes impressive effects of PEEP seen in experimental models.

The effects of PEEP in healthy lungs also result in discrepancies with the paradigm. In intact lungs, one would expect PEEP to produce overdistension and a lack of significant cyclic recruitment; however, even in this setting, PEEP reduces VILI. One study showed that adding PEEP in intact rats ventilated with very high Vt could reduce injury [14]. These findings have a clinical correlate: a recent randomized trial showed in patients without lung injury that ventilation with PEEP did not worsen outcome, but improved oxygenation and decreased the risk of ventilator-associated pneumonia [20].

The effect of Vt on healthy lungs is also controversial. In experimental settings, a Vt of 10 to 15 ml/kg results in pressures of around 10 to 20 cmH_2O and can induce substantial damage in a short time [21]. A classic experiment from Mascheroni and colleagues demonstrated that, even in spontaneously breathing animals, chemically-induced hyperventilation could trigger substantial lung damage [22]. This work highlights the importance of tissue deformation, represented by increased transpulmonary pressures, even during negative-pressure ventilation (absence of high alveolar pressure, more homogeneous inflation). Again, the significance of these findings in clinical practice is not so clear. Studies that have addressed this issue in surgical patients have found no differences in the lung inflammatory response or outcome between low Vt or high Vt with short ventilatory times (from 1 to 3 hours) [23,24], but found that high Vt increases proinflammatory mediators with longer ventilatory times [25-27]. Moreover, observational data [28,29] and recent clinical trials [30,31] suggest that high Vt increases the risk of acute lung injury in critically ill patients. The absence of specific markers of ventilator-associated lung injury precludes insight into the mechanisms underlying these results, but data from these articles suggest that Vt is important even in the absence of relevant recruitment/derecruitment processes (as these were patients with healthy lungs) and overdistension (as pressures were below 30 cmH_2O).

Low EELV has proved safe in both animals and patients, and this approach has sometimes been termed permissive atelectasis. In a recent study using an isolated lung model, Fanelli and colleagues demonstrated that permissive atelectasis caused the same amount of lung injury as the open lung strategy and only subtle differences in apoptosis and ultrastructural changes favoring the open lung strategy [32]. In the clinical setting, mortality rates in descriptive studies for patients managed with a low-pressure strategy are similar to those in clinical trials [33]. Taken together, these data contradict the volutrauma/atelectrauma model, suggesting that other mechanisms could be responsible for VILI.

Alveolar instability and ventilator-induced lung injury

Breathing, airflow, and blood flow exert complex mechanical forces on the lung that can be classified in specific physical terms: *stress* is the force per unit area; *strain*, also called stretch or deformation, is the change in length in relation to the initial length; and *shear stress* is the force per unit surface area in the direction of flow exerted at the fluid–surface interfaces. When applied to respiratory physiology, stress has been defined as transpulmonary pressure, and strain defined as the relationship between Vt and EELV. Although Gattinoni and colleagues have used the volume at zero PEEP as the reference EELV [34], it is not clear how recruitment (an increase in lung volume without increasing strain) can affect these measurements.

A series of mechanisms transform the lungs from a highly unstable structure (comparable with air bubbles in soap) into a very stable one. The surfactant system, alveolar interdependence, collateral ventilation, extracellular matrix, and mechanical properties of the chest wall work together to avoid alveolar collapse. These mechanisms guarantee a minimal resting volume (functional residual capacity/EELV) at end-expiration and a large number of alveoli to distribute each Vt. The net result is that healthy lungs present minimal changes in their structure during ventilation and only minor variations in alveolar size and shape. Using *in vivo* microscopy, several authors demonstrated that the change in size of subpleural alveoli is negligible when the total lung capacity remains between 10 and 80% [35,36], although substantial heterogeneity remained during

alveolar expansion in normal lungs. Whereas some zones undergo only minimal changes in each breath, other zones undergo deformations of up to 20% of their length. This finding could have important consequences for VILI in healthy lungs.

Failure of any of the above-mentioned mechanisms leads to alveolar instability, understood as an excessive tissue deformation during each breath. Although this may be a vague term, and in fact the thresholds of stress and strain that lead to tissue injury are unknown, we will use it as a concept beyond the classic opening and closing hypothesis. In this sense, alveolar instability refers not only to tidal changes in aeration, but also to those circumstances of excessive lung tissue deformation irrespective of the alveolar initial status. This common mechanism could help to override the different hypothesis on lung injury induced by cyclic changes in lung aeration (that is, opening and closing of alveoli versus fluid and foam in airways and alveoli [37]). Most circumstances that increase alveolar instability also increase the risk of VILI. Whereas the current paradigm considers alveolar instability and VILI to be concomitant consequences of an unknown cause, we hypothesize that alveolar instability is the main mechanism in VILI. Lung injury increases alveolar instability, and alveolar damage starts in the unstable zones [19]; VILI could spread from these zones where tidal changes are more relevant. These zones are also present in healthy lungs, so this model could explain the induction of VILI in patients with and without previous lung injury.

Some studies have explored how ventilatory parameters influence lung deformation (Figure 1). Halter and colleagues demonstrated that changes in subpleural alveoli correlate directly to Vt and inversely to PEEP [38]. Interestingly, even with high Vt (up to 15 ml/kg), increasing PEEP levels from 5 to 20 cmH$_2$O decreased alveolar instability from 108% to 15%. Experiments performed in cells corroborate these findings. Using cell cultures submitted to cyclic stretch, Tschumperlin and colleagues showed that the magnitude of deformation was more important than the peak stretch in inducing cell death [39].

Excessive tissue deformation can also explain why healthy lungs ventilated with high Vt and moderate pressures develop lung injury. Vt promotes a time-dependent increase in alveolar instability that could lead to lung damage [40]. Retrospective clinical studies have found that high Vt increases the risk of lung injury [28,29], and a recent randomized clinical trial found a higher risk of ARDS with 10 ml/kg Vt than with 6 ml/kg Vt [30].

Considering alveolar instability as the main mechanism of VILI explains how PEEP may reduce VILI [38]. Even during ventilation with high Vt, PEEP can significantly reduce tidal changes in alveolar size. Valenza and
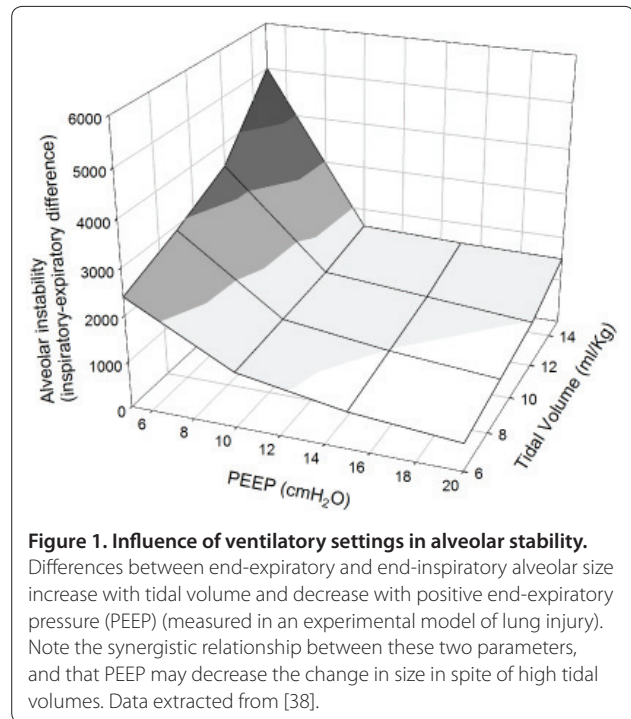

Figure 1. Influence of ventilatory settings in alveolar stability.
Differences between end-expiratory and end-inspiratory alveolar size increase with tidal volume and decrease with positive end-expiratory pressure (PEEP) (measured in an experimental model of lung injury). Note the synergistic relationship between these two parameters, and that PEEP may decrease the change in size in spite of high tidal volumes. Data extracted from [38].

colleagues found that VILI was delayed in intact rats ventilated with high airway pressures and PEEP [14]. One could hypothesize that PEEP avoids the progressive impairment in alveolar stability, as seen during *in vivo* microscopy studies.

Measurements of lung stability at the bedside

Explained in terms of stress and strain, ventilation with moderate/high PEEP and low Vt will reduce both stress (Vt) and strain (higher EELV induced by higher PEEP), thus reducing the risk of superimposed ventilator-associated lung injury. Terragni and colleagues found that even when Vt and plateau pressure are limited, patients with larger nonaerated lung compartments measured with computed tomography are exposed to tidal hyperinflation, with excessive lung deformation of the aerated compartment at each tidal breath [41]. Similarly, in patients with focal ARDS ventilated with the ARDSnet protocol, using a physiologic approach to PEEP setting based on the shape of the airway pressure curve as a function of time during constant flow attenuated alveolar hyperinflation [42]. Lack of lung recruitment with PEEP during protective lung ventilation is again associated with excessive lung deformation.

Chiumello and colleagues found that the plateau pressure and Vt were inadequate surrogates for lung stress and strain due to considerable overlap at both different Vt and PEEP values, and strain was clearly overestimated when recruitment was computed [34]. These results accounted for the high variability in functional

residual capacity (a hallmark of ARDS) and the ratio of lung elastance to total respiratory system elastance. Experimental models in which relatively low pressures may induce severe injury, discussed in previous sections, also reinforce this inaccuracy of airway pressures and volumes to estimate tissue injury, due to differences in specific lung and chest wall elastances. In this setting, only surrogates of stress and strain may help to minimize the damage induced by ventilation. When lung recruitability was taken into account, however, reducing the amount of opening and closing lung tissue by increasing PEEP yielded benefits that prevailed over the harmful effects of increasing alveolar strain [43]. Interestingly, opening and closing lung tissue was distributed mainly in the dependent and hilar lung regions and appeared to be an independent risk factor for death.

Reinterpreting the clinical trials

The ARDSnet trial on Vt demonstrated that overall survival is higher using a Vt of 6 ml/kg than using a Vt of 12 ml/kg at similar levels of PEEP; that is, similar lung volume at end-expiration [8]. We would expect much greater lung deformation in patients ventilated with higher Vt. Lowering Vt therefore not only reduces overdistension, but also improves alveolar stability.

Despite the controversy on how much high transpulmonary pressure a patient with ARDS can tolerate for how long and the sustained clinical benefits of this approach, very high plateau pressure in patients with ALI/ARDS and normal chest wall compliance can inflict direct damage to the lungs or can aggravate existing disease. Nevertheless, recent trials have challenged the concept that mortality decreases directly with reductions in plateau pressure. Several studies tested the effect of two levels of PEEP on patients with ALI/ARDS ventilated with low Vt [9,11-13]. At equal Vt, high PEEP resulted in higher plateau pressure at end-inspiration compared with low PEEP. Interestingly, despite the significant differences in plateau pressures, no differences in mortality were observed, and only a trend toward lower mortality and fewer complications among ARDS patients was observed in the high PEEP group.
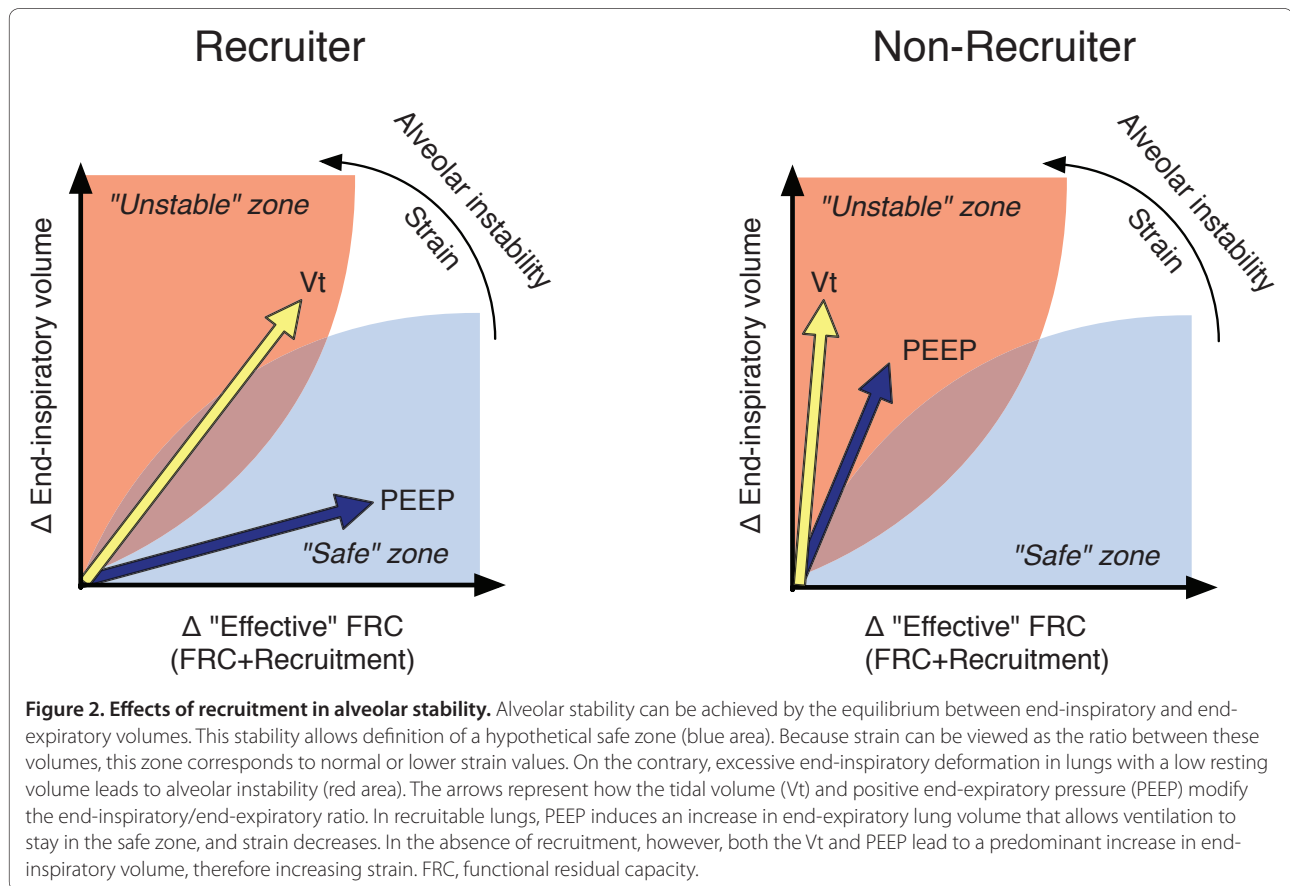
The benefits of high PEEP in ARDS patients were recently confirmed in a large systematic review and meta-analysis [44]. The patients included in these studies were exposed to similar stress, whereas strain depended on the previous effect of PEEP in the lung parenchyma (recruitment or overdistension). Figure 2 illustrates the differential effects of ventilatory parameters according to the presence of recruitment. In ALI/ARDS, the percentage of potentially recruitable lung is extremely variable and is strongly associated with the response to PEEP. This may also explain why the beneficial effects of PEEP are only seen in the most severe patients (that is, ARDS patients), in which recruitment and alveolar stabilization are the prevalent effects, whereas in those patients with mild injuries (ALI) this benefit is lost in the face of increased overstretching [44]. Unfortunately, prediction of the potentially recruitable lung using physiological variables that can be measured at the bedside is neither specific nor sensitive [45], and PEEP induces both recruitment and overdistension in most patients [46,47].

Increasing the complexity of the model

Although the main focus of the present review is to explain how the classic concepts of volutrauma and atelectrauma can be unified by understanding the effects of ventilatory parameters on lung structure and alveolar instability, mechanical ventilation can also have effects beyond the lung.

Intrathoracic pressures have a strong effect on hemodynamics, and Vt and PEEP can modulate right ventricular function, with consequences for lung injury [48]. Studies in experimental models of isolated ventilated and perfused heart–lung blocks have demonstrated that the lung hemodynamics may interact with tidal ventilation to modulate lung injury [49]. Inflation of the lungs above their functional residual capacity results in an increase in pulmonary vascular resistance [50], and the increase in vascular resistance is largely the result of compression of the alveolar microcirculation by a tidal increase in alveolar pressure and thus in extramural pressure. Tidal alveolar vessel compression is opposed by the alveolar vessel intramural pressure, which, everything else being equal, varies in parallel with left atrial pressure. In other words, an increase in or a reduction in left atrial pressure, respectively, opposes or enhances the alveolar vessel compression from positive pressure ventilation [51]. Recent data have given credit to the concept that lung vessels exposed to injurious ventilatory patterns behave like material prone to fatigue and failure in similar experimental conditions. It thus appears that both high and low capillary pressures are best avoided to limit the risk of VILI [49,51]. Moreover, these effects are aggravated by ventilation at rapid respiratory rates with concomitant increases of pulmonary artery pressure [52] and in conditions of high cardiac output [53,54]. In this context, PEEP serves to diminish transmural pressure (decreases strain) and attenuates edema formation and lung hemorrhage [48]. These data highlight the interactive nature of the processes and cofactors in the modulation of VILI-like global and/or regional pulmonary hemodynamics; the presence, type, and timing of secondary lung insults; and interactions between regional heterogeneity of pulmonary perfusion and regionally heterogeneous peak airspace strains. Lastly, these vascular variables also hint at potential difficulties in designing appropriate trials of lung-protective ventilatory strategies.

Figure 2. Effects of recruitment in alveolar stability. Alveolar stability can be achieved by the equilibrium between end-inspiratory and end-expiratory volumes. This stability allows definition of a hypothetical safe zone (blue area). Because strain can be viewed as the ratio between these volumes, this zone corresponds to normal or lower strain values. On the contrary, excessive end-inspiratory deformation in lungs with a low resting volume leads to alveolar instability (red area). The arrows represent how the tidal volume (Vt) and positive end-expiratory pressure (PEEP) modify the end-inspiratory/end-expiratory ratio. In recruitable lungs, PEEP induces an increase in end-expiratory lung volume that allows ventilation to stay in the safe zone, and strain decreases. In the absence of recruitment, however, both the Vt and PEEP lead to a predominant increase in end-inspiratory volume, therefore increasing strain. FRC, functional residual capacity.

Furthermore, mechanical ventilation can influence both local and systemic immune responses [1] because mechanical forces within the lungs trigger different biological responses that spread into the systemic circulation. Although much knowledge about this issue has been generated in recent years, the specific contribution of ventilator settings to the inflammatory response (that is, the biological activity brought about increasing volutrauma or atelectrauma) is unknown, and this complex response is likely to be influenced by patients' baseline conditions.

Conclusions

Knowledge of the mechanisms involved in VILI is important to develop ventilatory strategies that could result in clinical benefits. Recent advances suggest that isolated mechanical forces (plateau pressure, PEEP) cannot adequately explain VILI; rather, the amount of damage depends on the simultaneous interaction of these forces and the previous status of the lung parenchyma. Ultimately, dynamic changes in alveolar structure could be responsible for lung injury. The translation of these concepts to the bedside requires complex physiological reasoning and directed research.

Competing interests
The authors declare that they have no competing interests.

Abbreviations
ALI, acute lung injury; ARDS, acute respiratory distress syndrome; EELV, end-expiratory lung volume; PEEP, positive end-expiratory pressure; VILI, ventilator-induced lung injury; Vt, tidal volume.

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