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Lung Protection in Acute Respiratory Distress Syndrome: What Should We Target?

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Abstract

Purpose of Review: Most clinical trials of lung-protective ventilation have tested one-size-fits-all strategies with mixed results. Data are lacking on how best to tailor mechanical ventilation to patient-specific risk of lung injury.

Recent Findings: Risk of ventilation-induced lung injury is determined by biological predisposition to biophysical lung injury and physical mechanical perturbations that concentrate stress and strain regionally within the lung. Recent investigations have identified molecular subphenotypes classified as hyper- and hypo-inflammatory ARDS, which may have dissimilar risk for ventilation-induced lung injury. Mechanically, gravity-dependent atelectasis has long been recognized to decrease total aerated lung volume available for tidal ventilation, a concept termed the “ARDS baby lung.” Recent studies have demonstrated that the aerated baby lung also has non-uniform stress/strain distribution, with potentially injurious forces concentrated in zones of heterogeneity where aerated alveoli are adjacent to flooded or atelectatic alveoli. The preponderance of evidence also indicates that current standard-of-care tidal volume management is not universally protective in ARDS. When considering escalation of lung-protective interventions, potential benefits of the intervention should be weighed against tradeoffs of accompanying cointerventions required, for example deeper sedation or neuromuscular blockade. A precision medicine approach to lung-protection would weigh

Summary: A precision medicine approach to lung-protective ventilation requires weighing four key factors in each patient: biological predisposition to biophysical lung injury, mechanical predisposition to biophysical injury accounting for spatial mechanical heterogeneity within the lung, anticipated benefits of escalating lung-protective interventions, and potential unintended adverse effects of mandatory cointerventions.

Keywords

acute lung injury; acute respiratory distress syndrome; mechanical ventilation; ventilator-induced lung injury; precision medicine

INTRODUCTION

The vital importance of ventilation-induced lung injury (VILI) is striking. To date, all interventions found in a multicenter trial to improve survival from acute respiratory distress syndrome (ARDS) are thought to exert their effect by preventing VILI: lower tidal volumes [1,2], prone positioning [3], and, most controversially, neuromuscular blockade [4].

Equally striking is the small body of evidence to guide personalization of ventilatory support to patient-specific risk of VILI. Investigations historically have focused on pulmonary mechanics, providing invaluable insights for tailoring support to minimize mechanical stress both globally and regionally within the lung [5,6]. Increasingly, biological heterogeneity also is recognized as a clinically important factor in assessing VILI risk [7-9], although bedside ascertainment remains a challenge [10]. Integration of both biological and mechanical predisposition to VILI, weighed against risks of the lung-protective therapy and mandatory co-interventions, is essential for titrating ventilatory support to optimize therapeutic benefit.

BIOLOGICAL HETEROGENEITY AND VILI RISK

Biological heterogeneity has long been recognized as a central feature of ARDS. Trajectory of the ARDS patient unquestionably depends in part on ARDS risk factor [11-13]. Historical subtyping of ARDS often has classified patients by perceived precipitant, as “direct” or “indirect” lung injury [14]. Subsequent work identified molecular biological differences [15] and dissimilar genetic predisposing correlates [16] of direct versus indirect ARDS, but this classification scheme fails to account for severity or duration of risk exposure, leaving obvious residual within-class heterogeneity.

More recently, novel modeling approaches have identified two distinct molecular subphenotypes, hyperinflammatory and hypoinflammatory ARDS [8]. Post-hoc analyses of multiple clinical trials suggest subphenotypes classified in this manner may exhibit differential response to therapies [8,17,18], raising the prospect that they may also predispose differentially to VILI.

A detailed review of ARDS subphenotyping was published recently elsewhere in this journal [7].

MECHANICAL DETERMINANTS OF VILI

The mechanical determinants of VILI are best understood in terms of stress and strain. Mechanical stress is defined as the force per unit area within an object that occurs due to an externally applied force. Strain is a measure of deformation, the change in shape relative to its resting form. All currently described mechanical phenomena precipitating VILI can be framed in these terms.

Since lung insufflation is managed from a single airway opening at the endotracheal tube, mechanical ventilation targets historically have emphasized global mechanics, using whole-lung pressure and volume changes as surrogates of stress and strain, respectively [19,20]. The preponderance of preclinical and human literature now support a central role for

regional mechanical perturbations in VILI pathogenesis as well [21-24]. Indeed, much of what has been understood previously as stress/strain acting global across the lung, including hyperinflation from high tidal volumes, is correctly depicted only through consideration of regional mechanics.

Aerated Lung Volume is Reduced in ARDS

In patients with ARDS, global mechanics are grossly abnormal: higher airway pressures occur regularly despite modest tidal volumes. This lower respiratory system compliance has often been interpreted as stiffness, but in fact functional volume loss appears to be the main driver. The added weight of cell-rich pulmonary edema fluid, paired with inflammation-associated surfactant deactivation, causes gravity-dependent atelectasis, a classic finding on computed tomography of many ARDS patients. Thus, the functional aerated volume of the ARDS lung is *smaller* than normal, a phenomenon often termed the “ARDS baby lung” [25,26].

Importantly, compliance of the still-aerated lung volume, termed specific compliance (compliance normalized to volume of functional aerated lung) appears relatively preserved [25,27,28]. Because atelectatic lung tends to stay collapsed during tidal insufflation [29-31], volume is distributed almost entirely to the aerated baby lung (Figure 1). This aerated baby lung may readily suffer overdistension given its near-normal specific compliance.

The smaller aerated lung volume available for tidal ventilation provides compelling mechanism of action for lower tidal volumes. This rationale was noted explicitly in the ARDS Network tidal volume trial: “Since atelectasis and edema reduce aerated lung volumes in patients with [ARDS], inspiratory airway pressures are often high, suggesting the presence of excessive distension, or ‘stretch,’ of the aerated lung” [2].

Yet, this mechanistic understanding also highlights a key shortcoming of the current standard-of-care approach to tidal volumes. Targeting 6 ± 2 mL/kg *predicted* body weight for height and sex scales tidal volume to presumed *healthy* lung size, which, depending on degree of atelectasis in the ARDS lung, can yield wildly different exposure to stress and strain [19,32].

A precision medicine approach instead would scale tidal volumes to *functional* lung size, i.e. the ARDS baby lung volume [33-36].

Spatial Heterogeneity of Stress/Strain Distribution in ARDS

Stress and strain are spatially heterogeneously distributed within the aerated ARDS baby lung. Neighboring alveoli share an interalveolar septum and thus are mechanically interdependent. When one alveolus becomes fluid-filled or collapsed, the neighboring alveolus also is deformed [21]. This phenomenon has been observed in real-time via confocal microscopy, wherein shrinkage of a single fluid-filled alveolus causes the interalveolar septum to stretch and bulge into that fluid-filled space, producing deformation and local overexpansion of the adjacent air-filled alveolus. During insufflation, near the flooded alveolus, air-filled alveoli become more deformed, presumably predisposing to mechanical failure from high shear stress/strain [37] (Figure 2). Through a similar

mechanism, shear stress on aerated lung at the border of regional atelectasis may be orders of magnitude greater than elsewhere in the lung due to alveolar mechanical interdependence [21,24], a mechanism by which ventilation at low absolute lung volumes seemingly paradoxically can cause VILI [38].

The pulmonary radiographic correlate of this special heterogeneity may be the diffuse but patchy “ground glass” opacities on computed tomography. In vivo studies in animals and humans have found heterogeneous consolidation correlate strongly with markers of high regional strain [22,24], which map to regional lung inflammation [23,39-41], and are associated with elevated plasma markers of alveolar epithelial injury [42].

A precision medicine approach therefore would also seek to minimize spatial heterogeneity of stress/strain distribution when present, precisely the purported mechanism of benefit of prone positioning [43-47].

High Shear Stress/Strain in Small Airways

High shear forces may occur in small airways and alveolar ducts susceptible to tidal opening and collapse [48]. Inflammation-mediated surfactant dysfunction and edema weight favor small airways collapse at low lung volumes, particularly in gravity-dependent zones [49-51]. During inspiration, collapsed but recruitable lung units may assume an unzipping-like conformation as the air bolus propagates along the airway, generating high local shear forces that may be injurious [52-55]. It has been proposed also that creation and rupture of foam microbubbles at the air-liquid interface may generate high interfacial stress at the epithelial surface that contributes to lung injury [56-58]. Regardless of precise mechanism, the repetitive exposure to locally injurious forces with each inspiratory-expiratory cycle causes injury to small airways, often described as atelectrauma.

While it remains controversial the extent to which atelectrauma occurs and causes clinically significant injury in the non-ZEEP (zero end-expiratory pressure) era, a precision medicine strategy would minimize small airways stress/strain by identifying and mitigating atelectrauma. Preventing atelectrauma is an area for which precise PEEP titration, among other interventions, may offer benefit [59].

MECHANISMS OF ACTION FOR PROVEN VILI-PREVENTIVE INTERVENTIONS

All three interventions found in multicenter trials to improve survival in patients with ARDS share a common mechanism: prevention of VILI.

Lower tidal volumes directly mitigate overdistension of the aerated baby lung, decreasing plasma membrane wounding and rupture, disruption of cell junctions, and detachment of basement membranes [58,60-62]. Lower tidal volumes also attenuate shear strain from spatial mechanical heterogeneity by limiting the magnitude of shear deformation with each inspiratory cycle. Finally, lower tidal volumes may attenuate atelectrauma by decreasing likelihood of tidal recruitment with each inspiratory cycle.

Prone positioning distributes gravitational forces within the lung to favor ventral compression. Conformational shape-matching of the lung within the chest cavity favors ventral expansion regardless of position. Thus, with proning, gravitational and conformational forces act in opposing directions, yielding more homogenous aeration throughout the lung. Prone positioning therefore decreases shear strain and regional ventral hyperinflation [43,45,46]. To the extent that lung recruitment occurs, prone positioning also may mitigate atelectrauma [63].

Neuromuscular blockade prevents several patient-ventilator interactions that may cause mechanical injury. Inhibiting active inspiration may attenuate unintended high tidal volumes from breath stacking dyssynchrony [64,65] and transient regional hyperinflation from pendelluft [66]. Inhibiting active expiration may facilitate lung recruitment for a given PEEP by maintaining higher end-expiratory transpulmonary pressure, thereby decreasing atelectrauma [67]. Conflicting trial results around clinical efficacy of neuromuscular blockade in ARDS might be explained by differences in sedation management and dyssynchrony [4,68,69].

LUNG VERSUS PATIENT PROTECTION

Maximizing lung protection is not necessarily synonymous with maximizing patient benefit, even when the lung-protective intervention itself has a favorable side-effect profile. Most established lung-protective interventions require other therapies be instituted concomitantly to institute the lung-protective strategy. These *mandatory cointerventions* may carry their own untoward effects that change the risk-benefit calculation when therapeutic effect is framed not in terms of lung protection but rather the more appropriate target—net benefit to the patient (Table 1).

For example, lowering tidal volumes or permitting hypercapnia may increase patient discomfort and/or respiratory drive, which often are managed by increasing sedatives or analgesics [70]. Deep sedation also accompanies prone positioning as routinely instituted [3], and certainly neuromuscular blockade [4,68].

Excess suppression of respiratory drive may contribute to diaphragm disuse atrophy and respiratory muscle weakness that prolong invasive ventilation [71-74]. Regardless of its effects on drive, escalating sedation may impair extubation readiness, delay ventilator liberation, prevent early patient mobilization and physical therapy [74-76], unintended effects of mandatory cointerventions which may contribute to morbidity and mortality. Sedatives and analgesics may have medication-specific iatrogenic effects as well, including contributing to delirium, hemodynamic instability, and gastrointestinal complications [75-78].

Such tradeoffs of mandatory cointerventions may limit the role for so-called “ultra-low” tidal volume ventilation or “lung rest,” in which tidal volume and respiratory rate are reduced to levels prohibitive for maintaining adequate gas exchange without extracorporeal life support (ECLS). While a growing body of literature suggests tidal volumes below 6 mL/kg predicted body weight may confer additional *lung* protection [79-81], the extent to

which the totality of interventions required for ultra-low tidal volume strategies benefits patients again likely depends on potential downsides of ECLS, including bleeding, hemolysis, limb ischemia, immobility, infection, and unknown pharmacokinetic effects of key medications [82-84]. As cumulative experience refines ECLS management, risks may decrease, changing the risk-benefit calculation and potentially expanding populations for whom the net patient-level effect may be beneficial.

PROPOSED VENTILATION TARGETS

To be clear, existing data do not justify precise ventilation targets that are universally appropriate for all patients. There is no one-size-fits-all strategy for lung-protective ventilation. Rather, ventilation targets should be individualized according to clinical assessment of VILI risk, tradeoffs of cointerventions, and considering likely biological subphenotype [9,10]. For patients at low risk of VILI, strict adherence to the most protective ventilation targets often may be outweighed by adverse effects of cointerventions and a strategy of liberal targets with permissive dyssynchrony may be most appropriate. In contrast, for patients at highest risk of VILI, complete control of ventilation may be necessary to safely institute maximally protective ventilation despite the risks of associated cointerventions.

While several potential targets exist for lung-protective ventilation, they are not of equal importance. Cyclic stretch during tidal ventilation appears to be the most important driver of clinically significant lung injury [1,2,36,79,80]. Tidal volume per predicted body weight is the most widely used target but it does not scale to patient-specific aerated lung volume accounting for volume loss from atelectasis and consolidation (i.e. baby lung), and thus is increasingly recognized as an imperfect strategy [19,33,34,36]. Moreover, with patient-ventilator interactions such as double triggering and reverse triggering that lead to breath stacking dyssynchrony [64,85], volume-preset ventilator modes do not ensure the intended tidal volume is delivered in the patient with dyssynchronous spontaneous effort. Airway driving pressure (plateau pressure minus PEEP) has been advocated as a strategy for scaling tidal volume to respiratory system compliance and thus baby lung size [36]. Pressure-targeted, time-cycled ventilation targeting a specific driving pressure again risks misinterpretation if patient respiratory effort is not considered, as patient effort may augment transpulmonary pressure swings during tidal ventilation.

Also clearly important is the maximum global stretch experienced by the lungs during tidal ventilation. Airway plateau pressure, measured during a relaxed end-inspiratory pause, is most often used for this purpose, but there is no threshold effect for safety [86]. Plateau pressure fails to distinguish the contribution of lung versus chest wall recoil, and chest wall mechanics can vary widely between patients [87,88]. Transpulmonary pressure can be used to overcome this limitation and distinguish the contributions of lung from chest wall [89-91], but esophageal manometry is not widely available.

Proposed specific target ranges for several parameters relevant to lung-protective ventilation are presented in Table 2.

CONCLUSIONS: PRECISION MEDICINE FOR VILI

Personalizing lung-protective ventilation requires assessing each patient's risk of VILI and the risk/benefit of possible interventions to mitigate VILI. To gauge VILI risk, one must evaluate both biological predisposition and mechanical predisposition, including global and regional lung mechanics accounting for spatial heterogeneity of stress/strain distribution within the lung. The decision on whether to intervene to mitigate VILI risk additionally should include weighing the anticipated benefits of escalating lung-protective interventions against the potential unintended adverse effects of any mandatory cointerventions.

VILI in ARDS is an area ripe for precision medicine research. The field has multiple therapies proven to work in relatively heterogeneous trial populations and others with sound mechanistic plausibility but that have not proven successful in the broad trial populations in which they were studied. The field also has a reasonable understanding of mechanisms of action of proven therapies and a growing understanding of the biomechanical and molecular biological heterogeneity between patients. With recent technological advances, previously abstract concepts relegated to experimental protocols and theoretical models can now be measured at bedside. Electrical impedance tomography permits real-time bedside assessment of tidal recruitment and spatially heterogeneous ventilation [66,92-94]. Novel automated immunoassay devices [95,96] have made possible rapid (within 60–90 minutes) quantification of protein biomarkers known to fluctuate in response to VILI, raising the possibility that biological subphenotyping could be incorporated into clinical decision-making. Future research must decipher how best to integrate these additional data into clinical practice. Meanwhile, precision medicine can be practiced now doing what clinicians have always done: assessing patient-specific risk/benefit profile to deliver the right ventilation strategy at the right time.

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KEY POINTS

A precision medicine approach to lung-protective ventilation requires weighing four key factors in each patient:

- Biological predisposition to biophysical lung injury
- Presence and severity of spatial mechanical heterogeneity within the lung
- Anticipated benefits of escalating lung-protective interventions
- Potential unintended adverse effects of cointerventions, for example deeper sedation, required to escalate the lung-protective strategy

Figure 1. Functional aerated lung volume is decreased in ARDS.

As a result, the volume of aerated lung available for gas exchange and mechanical insufflation is reduced; this smaller aerated region is termed the baby lung. *Left:* CT chest of representative patient with ARDS. Ventral regions are well aerated with patchy ground-glass opacities and few areas of focal consolidation from pneumonia. Dorsal regions show dense dependent atelectasis caused by superimposed pressure from gravity on the edematous ARDS lung above. The effect of gravity on dependent atelectasis in the lung is analogous to that of gravity on a helical spring oriented vertically in gravity, such as observed with a Slinky™, the classic children's toy. The spring coils are distanced farther apart in non-dependent regions while the spring is near fully collapsed in gravity-dependent regions. Reprinted with permission [6]. *Right:* Measured inspiratory capacity is significantly reduced compared to their predicted normal values in patients with ARDS (mean difference, 29.5 ± 8.6 mL/kg predicted body weight [PBW]; $p < 0.001$). Box plots illustrate the median and interquartile range (boxes), mean (diamond), and maximum and minimum values (whiskers). Reprinted with permission [33].

Figure 2. Spatial heterogeneity increases stress and strain.

In the isolated perfused rat lung, confocal microscopy with optical sections 2 μm thick permits direct visualization of alveoli. *Top*: Adjacent alveoli share a common septum and are mechanically interdependent. In normal conformation, strain is minimized across neighboring air-filled alveoli. *Bottom*: In a single-alveolus model of pulmonary edema, the effects on local strain distribution of heterogeneous parenchymal consolidation and flooding can be appreciated. The liquid-filled alveolus shrinks due to micromechanical effects of meniscus formation. As a result, the adjacent air-filled alveolus bulges and overdistends. Reprinted with permission [37].

Table 1.

Potential adverse effects of cointerventions often employed with lung-protective strategies *

Cointervention	Associated Lung-Protective Strategies	Unintended Potential Adverse Effects
Deep sedation	Lower tidal volumes Prone positioning Neuromuscular blockade	Delayed spontaneous awakening trial Delayed spontaneous breathing trial Delayed mobilization and physical therapy Diaphragm disuse atrophy Hemodynamic instability Delirium
Neuromuscular blockade	Lower tidal volumes with dyssynchrony intolerance Prone positioning Neuromuscular blockade	All sedation-associated side-effects above Neuromuscular weakness
Extracorporeal life support	Ultra-low tidal volumes Lung rest	Catheter site hemorrhage Gastrointestinal hemorrhage Intracranial hemorrhage Limb ischemia Hemolysis and thrombocytopenia Delayed mobilization Infection

* For VILI-preventive interventions, the net therapeutic effect depends not only on the extent to which lung protection is afforded but also the unintended adverse effects of cointerventions routinely administered with the lung-protective strategy.

Table 2.Suggested targets for lung-protective ventilation according to VILI risk ^{*}

Parameter	Low VILI risk	High VILI risk	Priority
<i>Cyclic stretch</i>			
Tidal volume	6-8 mL/kg PBW	3-6 mL/kg PBW	Highest
Driving pressure	15 cm H ₂ O	10 cm H ₂ O	Highest
<i>Maximal stretch at end-inspiration</i>			
Plateau airway pressure	30 cm H ₂ O	27 cm H ₂ O	High
Plateau transpulmonary pressure [†]	20 cm H ₂ O	15 cm H ₂ O	High
<i>Spatial stress/strain heterogeneity</i>			
Prone positioning	Not currently recommended	Strongly recommended	High
PEEP	5-15 cm H ₂ O	10-24 cm H ₂ O	Moderate
End-expiratory transpulmonary pressure [†]	---	0-3 cm H ₂ O	Moderate
<i>Control of breathing</i>			
Patient-ventilator interaction	Permissive dyssynchrony	Consider synchronous ventilation	Moderate
P0.1 [‡]	> 1 cm H ₂ O	0-3 cm H ₂ O	Low
<i>Frequency of cyclic exposure</i>			
Respiratory rate	15-35 breaths/min	5-35 breaths/min	Low
<i>Gas exchange</i>			
Oxygen saturation	88-95 %	88-95 %	High
Arterial CO ₂	35-45 mm Hg	45-70 mm Hg	Low

^{*} Proposed target ranges and prioritization are based on available evidence at time of publication. They should be considered in context of the individual patient and adjusted accordingly based on clinically ascertained risk of ventilation-induced lung injury and cointerventions prescribed to help achieve targets.

[†] Where esophageal manometry is available to estimate pleural pressure and calculate transpulmonary pressure.

[‡] P0.1 is the airway occlusion pressure, the decrease in airway pressure during the first 100 msec (0.1 sec) of inspiration against an occluded airway.