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Ventilator-Induced Lung Injury

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INTRODUCTION

As with most medical and pharmacological interventions, mechanical ventilation must be titrated within a therapeutic window, providing the required life-sustaining support while minimizing unintended toxicity. The potential for mechanical ventilation to cause harm was first described in the mid-18th century.[1,2] John Fothergill postulated mouth-to-mouth resuscitation may be preferable to mechanical ventilation because “the lungs of one man may bear, without injury, as great a force as those of another man can exert; which by the bellows cannot always be determined”.[1] Over 250 years later, ventilator-induced lung injury (VILI) was proven definitively to contribute to mortality in patients with acute respiratory distress syndrome (ARDS).[3]

Classically, four mechanisms of VILI have been described: barotrauma, volutrauma, atelectrauma, and biotrauma (Table 1).[4] Recent recognition that heterogeneous regional mechanics, stress frequency, and pulmonary capillary stress failure may also contribute to VILI has inspired a renewed line of investigation toward personalizing lung-protective ventilation.

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DISCLOSURES

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CLASSIC MECHANISMS OF VILI

Barotrauma and Volutrauma

In 2000, the landmark ARDS Network trial demonstrated definitively that limiting tidal volume (6 vs. 12 mL/kg predicted body weight [PBW]) and plateau airway pressure (≤ 30 vs. ≤ 50 cmH_2O) improves survival in patients with ARDS.[3] This study and a small preceding pilot trial[5] brought into clinical practice what had been suggested for decades by preclinical studies—that mechanical ventilatory support with high volumes and pressures can *cause* preventable morbidity and mortality in critically ill patients.

Lung Volume & Transpulmonary Pressure—For much of the last thirty years, barotrauma (high inflation pressure-mediated lung injury) and volutrauma (overdistension-mediated lung injury) were viewed as distinct albeit related entities. In a classic study by Dreyfuss et al.,[6] rats were mechanically ventilated using one of three strategies: (1) high airway pressures and high tidal volumes; (2) high airway pressures and low tidal volumes; or (3) low airway pressures and high tidal volumes. The high-pressure low-volume strategy was achieved via thoracoabdominal strapping with rubber bands, decreasing chest wall compliance. Conversely, the low-pressure high-volume strategy was achieved via an iron lung (negative pressure ventilator). Animals supported with either high-volume strategy had markedly more severe lung injury compared to animals ventilated with the high-pressure low-volume strategy. Similar findings have been replicated in other animal models,[7–9] leading to the misleading conclusion that volutrauma is more important than barotrauma.[4,6,10]

It is true that high airway pressure per se does not cause VILI, as these studies confirmed. Yet, the pertinent distending pressure of the lungs is not simply the airway pressure, but rather the *transpulmonary pressure* (airway minus pleural pressure), the difference between the pressure inside versus outside the lung (Fig. 1).[11–13] Comparable transpulmonary pressures are achieved for a given lung volume regardless of whether airway pressure is positive (as during mechanical ventilation) or negative (as during normal spontaneous breathing).

Thus, lung volume and transpulmonary pressure are inherently related. In the Dreyfuss study, thoracoabdominal strapping in the high-[airway]-pressure low-volume group impeded chest wall excursion and thus assured both low lung volumes and low transpulmonary pressures. Conversely, in the low-[airway]-pressure high-volume group, iron lung negative pressure ventilation resulted in both high lung volumes and high transpulmonary pressures.

Failure to consider transpulmonary pressure in the mechanically ventilated patient can lead to miscalculating VILI risk. On one end, high airway pressures in morbid obesity in part may reflect transmitted high pleural pressures (i.e. low transpulmonary pressure) and not necessarily overdistension.[14,15] At the other extreme, the critically ill ARDS patient with air hunger and forceful spontaneous inspiratory muscle effort may have low airway pressures but large pleural and transpulmonary pressure swings and resultant tidal volumes, predisposing to barotrauma/volutrauma.[16]

Tonically Held vs. Cyclic Volumes & Pressures—The lungs appear to respond differently to high volumes and transpulmonary pressures depending on how they were achieved. In vitro models of alveolar type I and type II cells placed in a biaxial stretcher have demonstrated that cyclic strain (i.e. repeated, cyclic deformations) induce more cell death than a single, tonically held deformation of the same peak magnitude.[17,18] For a given peak strain, decreasing cyclic strain reduced the amount of cell death.

Analogous findings have been observed in vivo with animal models of VILI. High tidal volumes, with associated large cyclic strain, cause lung injury.[6,19,20] Yet, achieving the same peak strain with high PEEP and low tidal volumes, i.e. high end-expiratory lung volume and low cyclic strain, induces comparatively less lung injury.[21–23] Existing human data similarly suggest that VILI risk for a given end-inspiratory pressure and volume during mechanical ventilation may depend on the relative contributions of PEEP (tonically held deformation, less injurious) versus tidal volume (cyclic deformations, more injurious).[24–26] Translating these findings to clinical practice, if an upper limit on inspiratory pressure is exceeded, decreasing tidal volume rather than PEEP may afford additional lung protection.

Cellular Effects of Volutrauma & Barotrauma—The classic schema of alveoli as balloon-like structures that stretch during tidal inflation may not fully represent alveolar micromechanics. During normal breathing, alveolar walls themselves appear also to "unfold," minimizing elastic stretch and cellular strain except when lung volumes approach total lung capacity.[27–30] Deformation-related cell strain, when it does occur, induces rapid lipid trafficking to the plasma membrane, increasing cell surface area to prevent plasma membrane rupture and to repair the cell when stress failure does occur.[31–33] When these cytoprotective mechanisms are exceeded, additional inflation translates directly into cell strain, producing cell detachment from the basement membrane, epithelial and endothelial cell junction breaks, intracapillary blebs, and alveolar and interstitial edema, the microscopic correlates of clinical lung injury.[6,34]

Atelectrauma

In ARDS, surfactant dysfunction and weight of the edematous lung contribute to regional atelectasis.[35,36] Cyclic opening and collapse of such atelectatic but recruitable lung units during tidal ventilation contribute to lung injury termed atelectrauma.[36–38] For atelectatic alveoli, high shear stress is generated during recruitment at the interface between the air bolus and collapsed airway, causing mechanical injury (Fig. 2).[39,40] For flooded alveoli, formation and destruction of foam bubbles at the gas-liquid interface of flooded alveoli contributes additional local interfacial stress that disrupts plasma membrane-cytoskeletal adhesions and leads to lung injury.[41]

Clinically, low tidal volume ventilation may minimize atelectrauma by maintaining low airway driving pressures, decreasing likelihood of exceeding the critical opening pressure of collapsed lung units.[42] Additionally, PEEP set above the critical closing pressure of potentially collapsible lung units promotes sustained recruitment and may further prevent atelectrauma,[5,26,43–46] though the optimal PEEP titration strategy remains to be defined.

Biotrauma

Mechanical lung injury triggers an extensive biological response, including activation of a proinflammatory and pro-injurious cytokine cascade termed biotrauma.[23,47–49] This cascade may promote injury even in lung regions not faced with significant mechanical insult. Perhaps more importantly, this proinflammatory response also promotes extrapulmonary organ injury, predisposing to multiorgan failure that carries increased risk of death.[23,47–53]

The epithelial surface area of each adult lung is estimated to be 700–900 square feet,[54]nearly the size of one-half of a tennis court. Thus, in the lung, biological responses that are comparatively small in magnitude on a cellular level can precipitate collectively a substantial release of pro-injurious mediators. Compounding this signal amplification, roughly the entire blood volume of the human adult passes through the pulmonary circulation every minute. Thus, proinflammatory and pro-injurious mediators produced by the lung, upon entering the circulation, are readily transported throughout the body where they affect previously uninvolved organs. More than a theoretical construct, human ARDS clinical trials have confirmed that lung-protective ventilation indeed attenuates systemic inflammation[48,52] and extrapulmonary organ system failures (e.g. cardiovascular, renal, hepatic),[3,53] helping to account for their associated survival benefit.

REGIONAL MECHANICS

A seminal discovery shaping our current understanding of VILI occurred in the mid-1980s, when the first CT scans of patients with ARDS revealed strikingly heterogeneous lung parenchyma. In the classic CT for ARDS, patchy areas of well-aerated lung and poorly aerated lung are found in the ventral regions, with dense dependent atelectasis distributed in the dorsal posterior regions of the supine patient.[55–57] These radiographic discoveries suggest that (1) regional mechanics may vary throughout the ARDS lung; and (2) the total volume of aerated lung available to ventilate is reduced in size in patients with ARDS.

Lung inhomogeneity and shear strain

Differences in regional mechanics throughout the ARDS lung induce additional mechanical stresses that predispose to VILI. Neighboring alveoli are mechanically interdependent.[11,58] Collapse or flooding of one lung unit necessarily induces deformation of adjacent units as the interalveolar septum stretches inward toward the atelectatic or flooded unit. As a result, the adjacent air-filled alveolus experiences additional shear strain as it inflates non-uniformly (Fig. 3). Isolated, perfused animal lung models, wherein single-alveolus pulmonary edema is induced by micropuncture, have visualized this process with confocal microscopy.[58] In vivo animal models using PET have found [^{18}F]fluoro-2-deoxy-D-glucose uptake, indicating local neutrophilic activation, is increased in areas of high regional strain.[59] Initial human studies using PET CT similarly have confirmed lung inflammation to be heterogeneous in patients with ARDS, likely in part due to differences in regional strain.[60,61] These findings suggest a causal linkage to the association between parenchymal inhomogeneity and mortality observed in patients with ARDS.[62]

Both PEEP and prone positioning may reduce VILI in severe ARDS in part by improving lung homogeneity, yielding more uniform strain distribution.[63–67] Adequate PEEP minimizes small airways collapse, promoting sustained recruitment that improves lung homogeneity and increases total aerated lung volume available for tidal ventilation. PEEP may also redistribute edema fluid from the flooded alveolus into the interstitial space, decreasing shunt fraction while perhaps promoting more uniform interdependent alveolar mechanics.[68,69] PEEP appears to have mixed effects on pulmonary lymphatic flow, involved in clearance of extravascular lung water, depending on hemodynamic management and lung compliance.[70–72] PEEP has been shown in most ARDS animal models to protect against VILI.[6,22,37,49] Human studies with ARDS have yet to identify the optimal PEEP titration strategy,[43–45] though in general higher PEEP may be warranted in patients with more severe ARDS.[73] Most major clinical trials to date have adjusted PEEP based on oxygenation requirements using an arbitrary PEEP-FiO_2 titration table.[3,43,44,63,74–76] Yet, a PEEP titration strategy that seeks not only to maintain oxygenation but also to reduce regional strain may afford additional lung protection in patients with ARDS. Several such strategies have been tested in small clinical studies,[5,46,77–80] but none to date in a large multi-center trial adequately powered for patient-centered outcomes.

Prone positioning similarly appears to improve lung homogeneity. In the normal lung, alveolar size decreases from ventral to dorsal regions due to gravity and shape-matching of the lung and thoracic cavity.[35] Increased mass of the edematous ARDS lung generates a superimposed pressure on gravity-dependent lung regions,[35] leading to dense atelectasis of the dorsal lung regions with relative sparing of more ventral regions. When the patient is repositioned prone, shape matching again favors decreased alveolar size from ventral to dorsal regions, but the gravitational effect (non-trivial from edema weight in ARDS) now favors expansion of dorsal regions.[81] The net effect, as evidenced on CT, appears to be more homogeneous aeration throughout the lung,[66,81] likely promoting more uniform strain distribution and thus lung protection. Indeed, the recent PROSEVA multicenter randomized trial found that proning patients with early severe ARDS for at least 16 hours/day improved survival compared to semirecumbent supine positioning—despite management with identical lung-protective mechanical ventilation strategies.[63] While the effect size in PROSEVA may overestimate that of proning—due to more frequent use of neuromuscular blockade in the prone arm (which may afford additional lung protection[76]) and greater baseline vasopressor requirements in the supine arm—we believe proning does afford added lung protection in select patients with severe ARDS.

Although PEEP and proning share related physiological mechanisms, a mechanics-based PEEP titration strategy has not been studied adequately in a major trial of prone positioning. At least one physiological human study suggests concomitant proning and comparatively higher PEEP may further improve lung homogeneity relative to either strategy in isolation.[82] However, the extent to which a mechanics-based PEEP titration strategy affords additional clinical benefit during prone positioning, or vice versa, is unknown.[64]

The ARDS “Baby Lung”

In patients with ARDS, the weight of superimposed edematous lung tissue, coupled with surfactant dysfunction, contribute to dense atelectasis of dependent lung regions.[35,38,83] As a result, the volume of aerated lung available for gas exchange and mechanical insufflation is reduced, a concept termed the ARDS baby lung (Fig. 4).[84] The baby lung is not a fixed anatomical structure, as evidenced by redistribution of dependent atelectasis to ventral regions with prone positioning.[81,85] Nor does aerated lung equate to normal lung, as evidenced by enhanced [^{18}F]fluoro-2-deoxy-D-glucose uptake signaling active inflammation in aerated regions.[86]

Baby lung inspiratory capacity predicts end-inspiratory lung stress during tidal ventilation,[25] suggesting low tidal volumes may be effective in ARDS in part because the functional lung volume itself is reduced. Indeed, the original ARDS Network trial authors reasoned that lower tidal volumes may be required to prevent regional overdistension in ARDS in part because the aerated lung volume is reduced.[3] In vivo preclinical models using diffusion-weighted hyperpolarized gas MRI have found the aerated baby lung may experience regional overdistension.[87,88] An ideal lung-protective strategy might scale tidal volumes to functional baby lung size rather than predicted healthy lung size (i.e. mL/kg PBW). Such strategies have been explored in physiological studies[25,89,90] but have yet to be tested in prospective clinical trials powered for patient-centered outcomes.

STRESS FREQUENCY & PERMISSIVE HYPERCAPNIA

Both the magnitude *and frequency* of peak alveolar stretch likely to contribute to VILI.[91]Preclinical studies have found that, for a given magnitude of lung stretch, increasing the stretch frequency also worsens lung injury.[17,91–93] In human studies, infrequent high-volume breaths, such as occasional recruitment maneuvers or sigh breaths, do not appear to cause clinically significant lung injury[94] and may even afford transient lung protection.[95–98] At the other extreme, delivery of high tidal volumes with every breath clearly worsens VILI and mortality in patients with ARDS.[3,5] We speculate the dose-response curve for the relationship between frequency of high-volume breaths and VILI may be J-shaped. Occasional high-volume breaths, such as sighs, may be protective by preventing derecruitment,[96] increasing lung homogeneity,[97] and increasing baby lung size (maintained if PEEP exceeds small airways closing pressure).[25] However, frequent high tidal volumes cause VILI in at-risk patients.

The precise role for limiting stress frequency remains to be determined. Maintaining a low tidal volume strategy while also limiting stress frequency—by limiting respiratory rate—will result in hypercapnic acidosis, a strategy termed permissive hypercapnia.[5,99] This approach was shown in a small clinical trial to improve survival compared to a high tidal volume strategy.[5] However, permissive hypercapnia was not evaluated in the ARDS Network trial of high vs low tidal volumes,[3] which instead advised a high respiratory rate to achieve near eucapnia and normal pH. The high-respiratory rate strategy of the ARDS Network likely requires less sedation during low tidal volume ventilation than a permissive hypercapnia strategy. Because hypercapnic acidemia heightens respiratory drive, deep sedation or

neuromuscular blockade may be required to reinforce lung-protective ventilation and minimize patient-ventilator dyssynchrony during permissive hypercapnia.

Hypercapnia also has several biological effects of unclear clinical consequence. In preclinical VILI models, hypercapnic acidosis impaired alveolar cell migration[100] and plasma membrane repair[101] following mechanical injury, the latter in a pH-dependent fashion.[101] Hypercapnia, independent of pH, also may impair alveolar edema fluid clearance by promoting endocytosis of plasma membrane Na^+-K^+-ATPase channels involved in maintaining the Na^+ gradient that water follows.[102] Hypercapnia attenuates TNF-α, IL-1, IL-6, and IL-8 cytokine production, oxygen free radical formation, and NF-κB activation,[103–107] potentially limiting the cascading effects of biotrauma on pulmonary and extra-pulmonary organ failure. In vivo models of VILI,[108,109] bacterial pneumonia,[110] and abdominal sepsis[111] have demonstrated that hypercapnic acidosis, achieved via inspired CO_2, attenuates lung injury. Different experimental preparations have yielded conflicting results on the effects of hypercapnia in pulmonary infection,[112] highlighting the need for further translational research and ultimately clinical studies.

CAPILLARY STRESS FAILURE

In addition to alveolar epithelial injury, capillary endothelial stress failure likely contributes to VILI. Enhanced regional pulmonary blood flow, such as occurs from hypercapnic adrenergic tone or attempted ventilation-perfusion matching, increases capillary wall stress.[113] Multiple preclinical models have found that increasing pulmonary blood flow worsens lung injury.[113–116] Dynamic shear forces from blood flow appear to play a central role, as achieving high capillary pressure by raising left atrial pressure statically does not produce comparable lung injury.[115] Importantly, increasing pulmonary blood flow may lead to lung injury that otherwise would not occur during moderate tidal overdistension.[116]

The clinical implications to VILI from pulmonary capillary stress failure remain unclear. Vasoactive medications may have distinct effects on pulmonary blood flow and distribution and thus attenuate or exacerbate VILI.[117,118] A randomized clinical trial evaluating hemodynamic management for neuroprotection following severe head injury found increased ARDS incidence in the strategy requiring increased vasopressor use and intravenous fluid administration to achieve higher mean arterial and cerebral perfusion pressures.[119] Similarly, in a multicenter trial of patients with ARDS, a more liberal fluid management strategy was associated with fewer ventilator-free days compared to a strategy favoring earlier diuresis, although survival did not differ significantly between groups.[120] While capillary stress failure unquestionably plays a role in VILI, the magnitude of its importance and any clinical management decisions that should follow remain to be defined.

VILI PREVENTION IN PATIENTS WITHOUT ARDS

Perhaps the greatest challenge for VILI prevention, among patients without ARDS, is to balance the degree of VILI risk with the potential for harm from a given VILI prevention strategy. Clinical lung injury does not develop in most patients even when identifiable risk factors are present.[121,122] Clinical risk prediction scores such as the Lung Injury Prediction

Score (LIPS)[122] and Early Acute Lung Injury Score[123] perform reasonably well in identifying patients at-risk of lung injury, but have yet to prove useful in guiding preventive strategies. A multiple-hit conceptual model for VILI risk has been proposed, wherein patients with increased baseline risk for lung injury (e.g. from pneumonia or sepsis) are likeliest to develop clinical lung injury if secondary insults are encountered (e.g. exposure to high tidal volumes).[124]

Among candidate interventions for VILI prevention in patients without ARDS, limiting tidal volume has been most widely studied. A two-hospital randomized trial found decreased ARDS incidence with 6 versus 10 mL/kg PBW in critically ill non-ARDS patients with anticipated need for mechanical ventilation of more than three days, although survival and ventilator-free days did not differ.[125] A multicenter trial of intraoperative low tidal volumes among high-risk patients undergoing abdominal surgery found decreased need for postoperative positive pressure ventilation and shorter hospital length of stay with 6–8 mL/kg PBW compared to 10–12 mL/kg PBW.[126] Building on these findings, a recent meta-analysis of 15 small randomized trials and 5 large observational studies similarly concluded lower tidal volumes targeting 6–8 mL/kg PBW were associated with improved survival in patients without ARDS.[127] However, attempts to restrict tidal volume may prove challenging in patients supported in assist-control or pressure-support modes[128,129] without increasing sedation or even administering neuromuscular blockade to blunt patient inspiratory effort. Careful evaluation of the costs from such co-interventions must be addressed before broadly recommending low tidal volumes for all.[130] This balance may be easier to strike for intraoperative low tidal volumes among high-risk patients because general anesthesia and neuromuscular blockade are routine in many major surgeries. Ideally, tidal volume limits might be individualized for each patient according to VILI risk and level of co-interventions (e.g. sedatives, paralytics) required to achieve them.

SUMMARY

Prevention of VILI can attenuate multiorgan failure and improve survival. Clinically significant VILI may occur from volutrauma, barotrauma, atelectrauma, biotrauma, and shear strain. Differences in regional mechanics play an increasingly recognized role in VILI pathogenesis and prevention. Less well understood are the contributions of alveolar stress frequency and pulmonary capillary stress failure, though both have compelling biological plausibility. Increased understanding of VILI has led to several preventive strategies targeting underlying mechanisms (Table 2). VILI occurs most readily in patients with concomitant physiological insults (e.g. sepsis, trauma, major surgery) that prime the immune system for a cascading response to mechanical lung injury. Because the majority of non-ARDS patients at risk of VILI do not develop clinically significant lung injury,[121,122] prevention efforts should carry minimal side-effects to justify broad application or be targeted to subsets of patients at increased risk.

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SYNOPSIS

Prevention of ventilator-induced lung injury (VILI) can attenuate multiorgan failure and improve survival in at-risk patients. Clinically significant VILI occurs from volutrauma, barotrauma, atelectrauma, biotrauma, and shear strain. Differences in regional mechanics play an increasingly recognized role in VILI pathogenesis. Several interventions targeting these mechanisms are available to protect against VILI. However, most patients at risk of lung injury do not develop VILI. Current evidence supports the multiple-hit hypothesis, which states that VILI occurs most readily in patients with concomitant physiological insults (e.g. sepsis, trauma, major surgery) that prime the immune system for a cascading response to mechanical lung injury. VILI prevention strategies must balance risk of lung injury with untoward side-effects from the preventive effort, and may be most effective when targeted to subsets of patients at increased risk.

KEY POINTS

- Prevention of ventilator-induced lung injury (VILI) can attenuate multiorgan failure and improve survival in at-risk patients.
- Clinically significant VILI occurs from volutrauma, barotrauma, atelectrauma, biotrauma, and shear strain. Differences in regional mechanics play an increasingly recognized role in VILI pathogenesis.
- VILI occurs most readily in patients with concomitant physiological insults (e.g. sepsis, trauma, major surgery) that prime the immune system for a cascading response to mechanical lung injury.
- VILI prevention strategies must balance risk of lung injury with untoward side-effects from the preventive effort, and may be most effective when targeted to subsets of patients at increased risk.

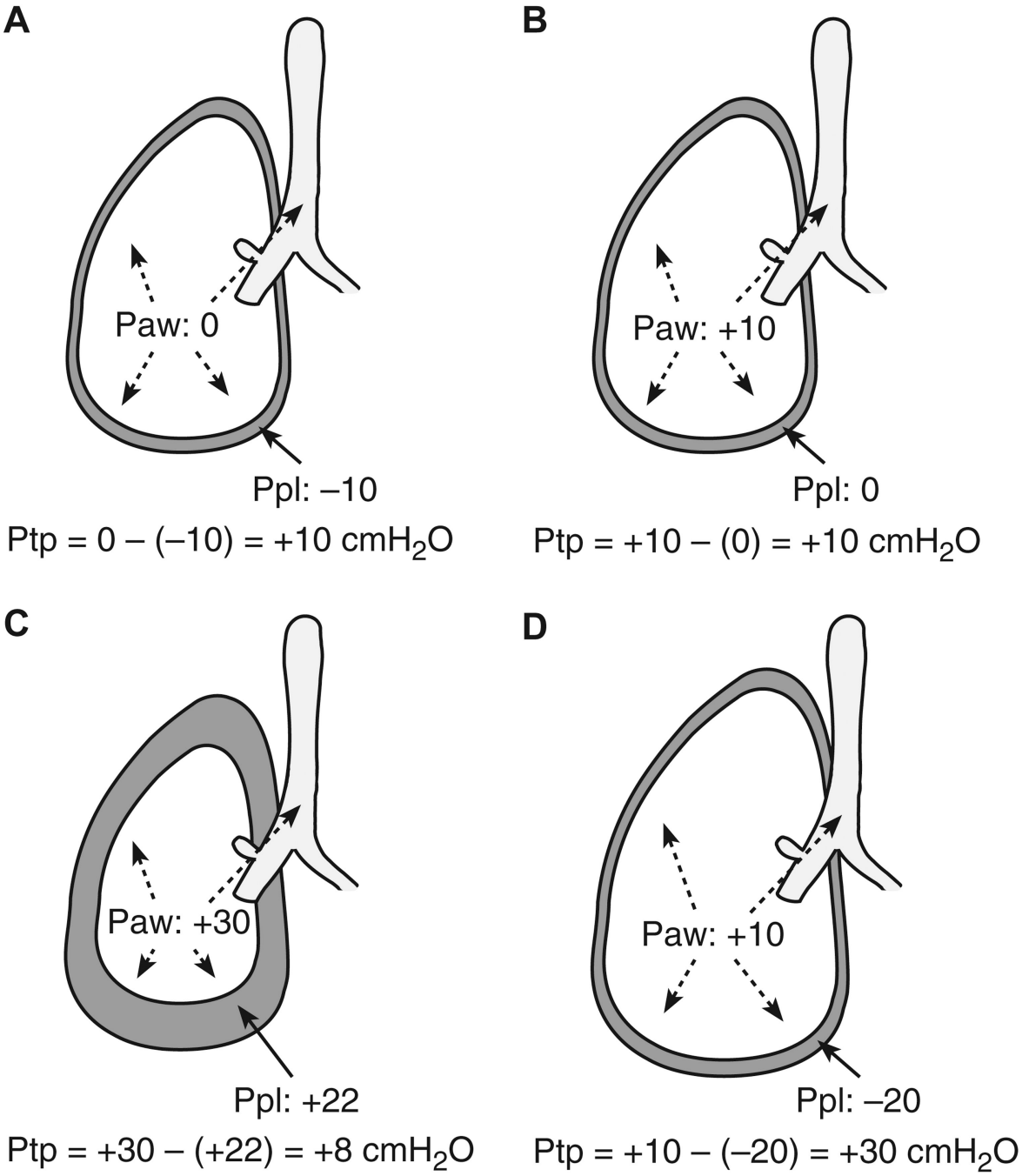

Figure 1. Transpulmonary pressure

Transpulmonary pressure ($P_{airway} - P_{pleural}$) is the pertinent distending pressure of the lung. At zero flow, airway and alveolar pressure are equal, for example during an end-inspiratory plateau pressure maneuver. (a) Non-intubated patient, normal spontaneous breathing at end-inspiration. (b) Intubated patient without respiratory disease, passive on mechanical ventilator at end-inspiration. (c) Intubated patient, chest wall stiffness results in lower transpulmonary pressure and lower lung volume at end-inspiration despite higher airway pressure. (d) Intubated patient, forceful inspiratory muscle effort, such as from heightened

respiratory drive, produces high transpulmonary pressure and lung volume at endinspiration even though airway pressure is reasonably low. *Abbreviations*: Paw, airway pressure; Ppl, pleural pressure; Ptp, transpulmonary pressure.

Adapted from Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J Med 2013;369(22):2126–36; with permission.

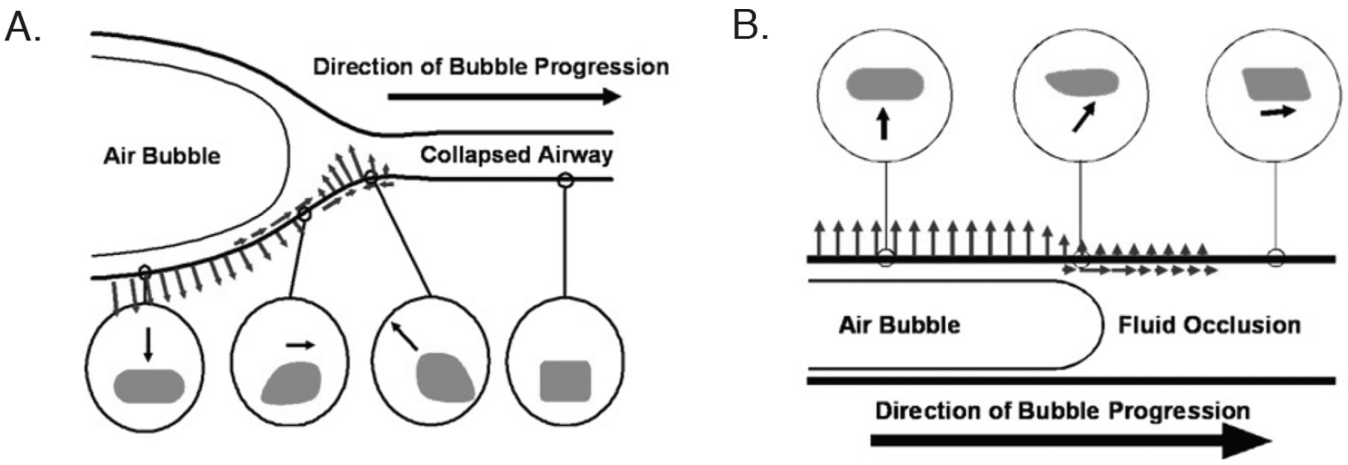

Figure 2. Atelectrauma

Local stress and strain of epithelial cells generated during alveolar recruitment. (a) Air bubble propagation down atelectatic airway generates dynamic wave of shear stress and strain at interface of air bubble and collapsed airway. As the air bubble approaches, the epithelial cell is pulled inward toward the bubble. As the air bubble passes, the cell is pushed outward. (b) Air bubble generates similar shear stress and strain of epithelial cells during propagation along flooded airway.

From Ghadiali SN, Gaver DP. Biomechanics of liquid-epithelium interactions in pulmonary airways. Respir Physiol Neurobiol 2008;163(1–3):232–43; with permission.

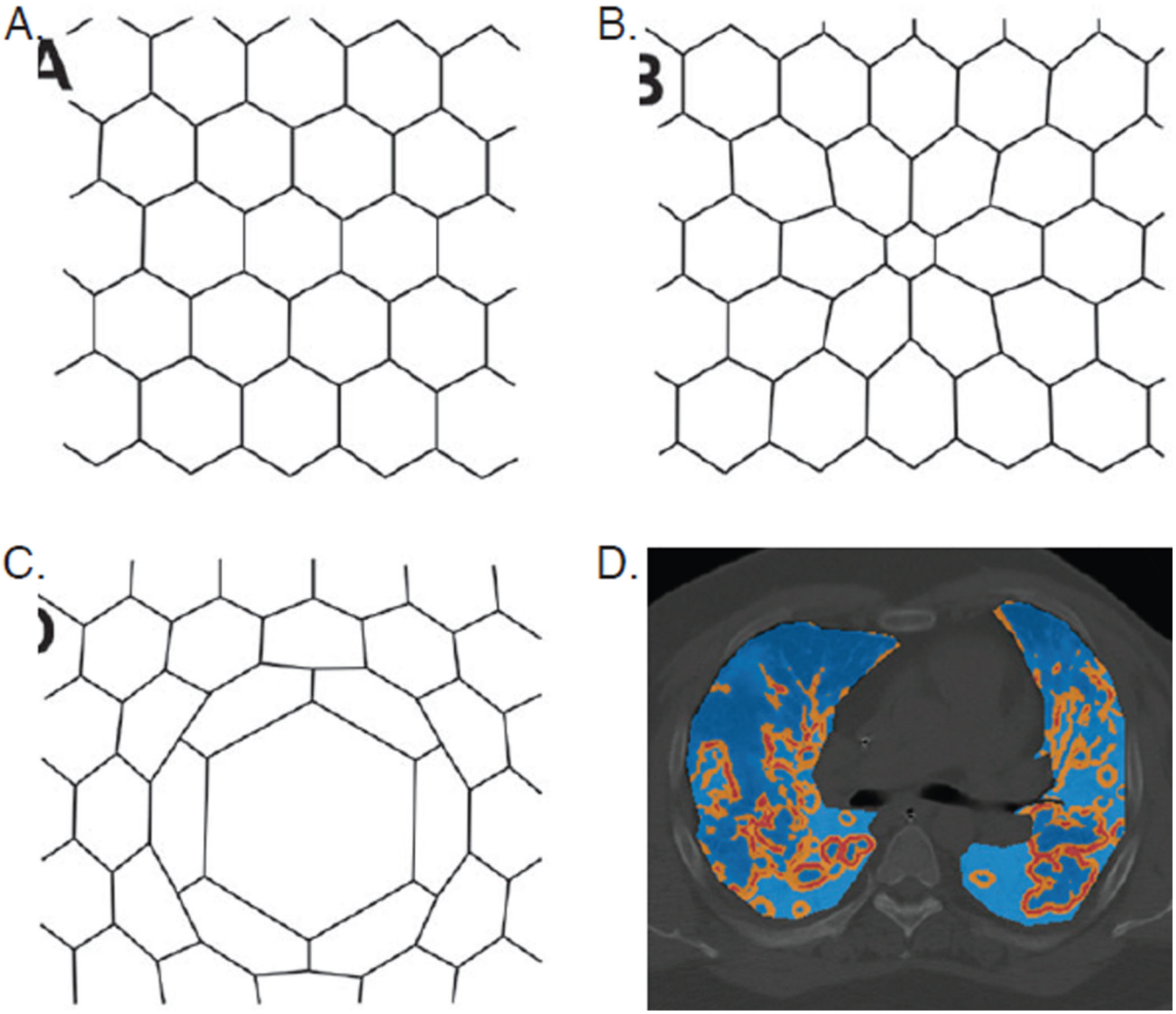

Figure 3. Mechanical alveolar interdependence and shear strain

A–C: classic model of alveolar interdependence; each hexagon represents an alveolus in cross-section. (a) Homogeneous alveolar inflation minimizes strain. (b) Atelectasis of center alveolus induces shear strain of neighboring alveoli. (c) Asymmetric inflation of center alveolus induces shear strain of neighboring alveoli. (d) CT chest with overlying map of CT-derived regional stress concentration due to parenchymal heterogeneity in a representative patient with ARDS (*light blue*: low stress; *orange*: moderate stress; *red*: high stress).

Figure 3A–3C from Mead J, Takishima T, Leith D. Stress distribution in lungs: a model of pulmonary elasticity. J Appl Physiol 1970;28(5):596–608. Reprinted with permission of the American Physiological Society; copyright © 2016 American Physiological Society. Figure 3D from Cressoni M, Cadringher P, Chiurazzi C, et al. Lung inhomogeneity in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2014;189(2):149–58.

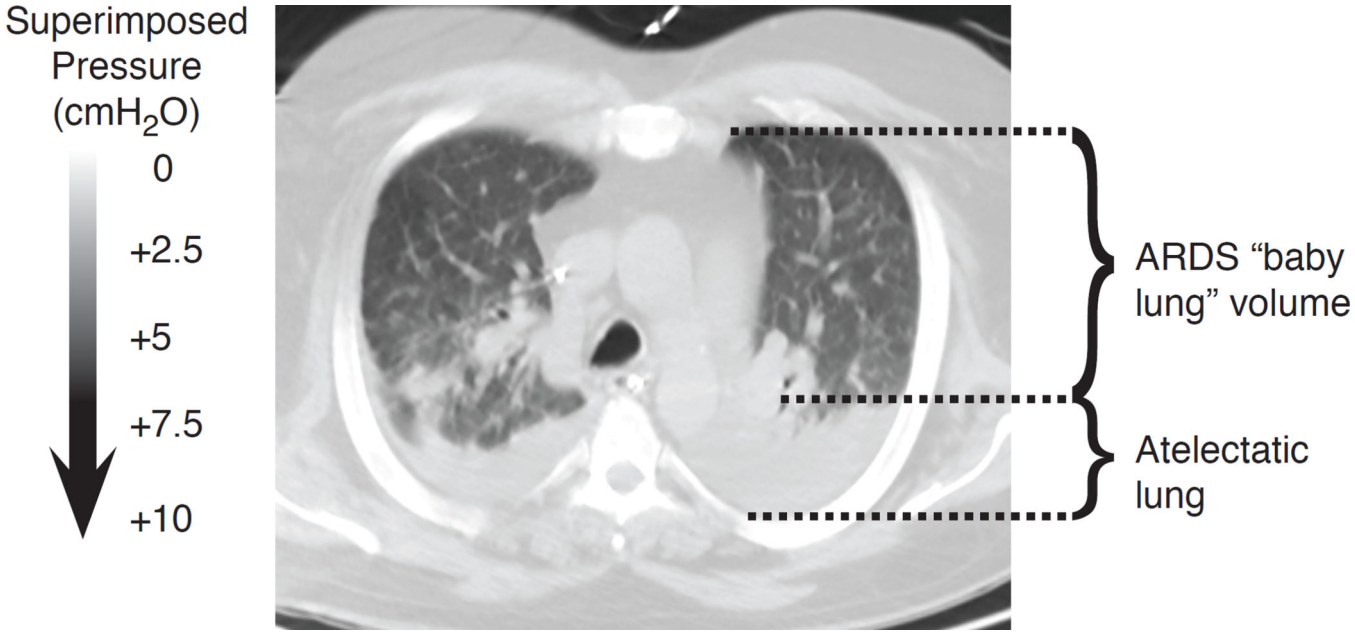

Figure 4. ARDS baby lung

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 exhibit dense dependent atelectasis due to superimposed pressure from gravity on the edematous ARDS lung above. As a result, the volume of aerated lung available for gas exchange and mechanical insufflation is reduced—termed the “baby lung.”

Table 1

Definitions of Key Terms Frequently Encountered in Literature

Term	Definition
Atelectrauma	Lung injury caused by high shear forces from cyclic opening and collapse of atelectatic but recruitable lung units.
Baby lung	Conceptual model for the reduced volume of non-atelectatic aerated lung available for tidal insufflation and gas exchange in patients with ARDS.
Barotrauma	Lung injury caused by high transpulmonary pressure. May occur even at lower airway pressure if pleural pressure is extremely negative (e.g. forceful inspiratory effort).
Biotrauma	Additional lung and extra-pulmonary organ injury caused by pro-injurious inflammatory response to mechanical lung injury.
Compliance	Change in volume for a given change in pressure. May refer to respiratory system compliance ($\Delta V/\Delta P_{airway}$), lung compliance ($\Delta V/\Delta P_{transpulmonary}$), or chest wall compliance ($\Delta V/\Delta P_{pleural}$). Respiratory system compliance reflects contributions of both the lung and chest wall, and is often incorrectly labeled as lung compliance in the literature.
Elastance	Change in pressure for a given change in volume, also called stiffness. Inverse of compliance.
Lung inhomogeneity	Differences in regional lung mechanics owing to mechanically interdependent interalveolar septae shared between aerated alveoli and adjacent fluid-filled or atelectatic alveoli. Results in high regional shear strain. Manifested on CT scan as regions of well-aerated lung adjacent to patchy ground-glass opacities and atelectasis.
Shear strain	Angular deformation of an object relative to its resting conformation. As example, if resting object is square-shaped, shear strain would produce an oblique-angled rhombus.
Strain	Change in size/shape of an object relative to its resting size/shape, expressed as ratio of displacement magnitude divided by reference size. Calculation of lung strain in the mechanically ventilated patient is controversial because ideal resting size/shape of the diseased lung is unclear.
Stress	Internal forces per unit area that balance an external load. Lung stress is represented by the transpulmonary pressure.
Transpulmonary pressure	Pressure difference inside versus outside the lung ($P_{TP} = P_{airway} - P_{pleural}$), which is the pertinent distending pressure of the lung. Airway and alveolar pressure are equal at points of zero-flow.
Volutrauma	Lung injury caused by alveolar overdistension.

Table 2

Strategies for VILI Prevention in At-Risk Patients

Preventive Strategy	Implementation	VILI Mechanisms*	
Limit tidal volume	Scaled to healthy lung size[3,5,42] (≤ 8 mL/kg PBW) or functional lung size.[25,89] Scaling to functional lung size may be ideal, but strategy not yet well defined.	•	Prevent tidal overdistension (volutrauma)
		•	Decrease cyclic and end-inspiratory stress (barotrauma)
		•	Minimize shear forces via smaller-volume inflation of aerated alveoli adjacent to flooded/atelectatic alveoli
		•	Prevent tidal recruitment of atelectatic alveoli (atelectrauma)
Limit inspiratory pressure	Limit airway plateau pressure,[3] airway driving pressure,[5,131] or transpulmonary driving pressure.[25,46,89] Limiting transpulmonary driving pressure may be ideal, but strategy not yet well defined.	•	Identical mechanisms as with limiting tidal volume
PEEP	PEEP-FiO_2 table,[43,44] maximal static stress (Express),[45] esophageal pressure-guided,[46] highest respiratory system compliance,[79] lower inflection point of pressure-volume curve.[5] Mechanics-based approach to PEEP may be ideal, but optimal strategy not yet well defined.	•	Increase aerated functional lung size to prevent tidal overdistension (volutrauma)
		•	Maintain transpulmonary pressure higher than closing pressure to prevent tidal collapse during expiration (atelectrauma)
		•	Improve lung homogeneity to decrease shear strain
		•	Decrease pulmonary blood flow to attenuate capillary stress failure
Prone positioning	In severe ARDS, prone at least 16 hours daily.[63] No clinical data to suggest efficacy as rescue therapy.	•	Improve lung homogeneity to decrease shear strain
		•	Increase aerated ARDS baby lung size (volutrauma)
Limit respiratory rate	Adjust to maintain minimum allowable pH or maximum allowable $PaCO_2$.[5] May require deep sedation, neuromuscular blockade, or extracorporeal CO_2 removal. Not proven in clinical trial vs. high-rate strategy.	•	Limit stress frequency, reducing exposure to volutrauma, barotrauma, atelectrauma, and cyclic strain
		•	Unclear net effect of resultant hypercapnia
Limit spontaneous respiratory effort	In severe ARDS, increased sedation ± neuromuscular blockade.[76]	•	Limit inspiratory effort to prevent occult high tidal volumes from breath stacking
		•	Limit forced expiration to prevent cyclic derecruitment (atelectrauma)

*Preventing mechanical lung injury decreases biotrauma.