Mechanisms Of Lung Injury

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Introduction

Lung injury can arise from direct chemical exposure, infectious disease, dysregulated inflammatory responses, and immunological derangements. While the different mechanisms target various components of the alveolo-capillary unit, they lead to a final common pathway of epithelial/endothelial damage and dysregulated inflammation. These injuries create a vulnerable respiratory system, increasing its susceptibility to secondary injury from the physical forces of mechanical ventilation (barotrauma, volutrauma, atelectrauma, biotrauma, and ergotrauma). Similarly, injurious physical forces can be generated by the patient's own respiratory effort during spontaneous breathing, known as patient self-inflicted lung injury (P-SILI).

The primary objective of invasive mechanical ventilation is to reduce the workload of the respiratory muscles while maintaining adequate gas exchange. However, excessive mechanical energy can itself inflict damage, leading to ventilator-induced lung injury (VILI) an acute injury to the airways and parenchyma caused or exacerbated by mechanical ventilation. To fully appreciate the context and pathophysiology of VILI, it is essential to understand the broader spectrum of insults that can compromise alveolar integrity.

This chapter will first delineate key non-mechanical mechanisms of acute lung injury–chemical, inhalation, infectious, inflammatory, and immunologic–followed by a detailed review of the pathophysiology, physiological impacts, and evidence-based prevention strategies for both VILI and P-SILI. Understanding this continuum from primary insult to secondary VILI and P-SILI is fundamental to optimizing lung protective strategies in mechanically ventilated patients.

Non-Mechanical Pathways to Acute Lung Injury

Primary lung injury arises from direct insults that compromise the integrity of the alveolo-capillary unit. While diverse in etiology, they share a common final pathway of increased alveolar permeability, edema, inflammation, and impaired gas exchange.

Chemical Lung Injury

Aspiration pneumonitis, also known as Mendelson syndrome, results from the aspiration of sterile gastric contents. The acidic contents inflict a direct caustic injury to the alveolar-capillary interface, immediately increasing its permeability. Experimental studies have established that the severity of injury is pH-dependent, with a threshold of pH < 2.5 and a volume exceeding 0.3 ml per kilogram of body weight required to induce a clinically significant injury. The primary chemical insult is followed by a secondary inflammatory response mediated by activation of the innate immune system via Toll-like receptors (TLR4), recruiting neutrophils and promoting release of proinflammatory mediators (e.g. TNF-α, IL-8). This cascade amplifies the initial permeability defect, resulting in protein-rich pulmonary edema.

Unlike infectious pneumonia, the initial insult is sterile, as gastric acid typically prevents bacterial growth. However, secondary infection may supervene in the days following injury. Furthermore, gastric colonization by pathogenic organisms can develop in patients receiving enteral feeds, those on acid-suppressive therapy (histamine-2 receptor antagonists or proton pump inhibitors), and individuals with gastroparesis or small bowel obstruction. In these circumstances, lung injury may arise from a hybrid pathophysiology: the initial chemical pneumonitis, superimposed with bacterial infection and the associated inflammatory response.

Inhalation Lung Injury

Inhalation injury refers to the direct damage of the respiratory tract from smoke, heat, or chemical irritants. Smoke inhalation in burn victims is the most encountered form of this injury, and its pathophysiology is distinct from other mechanisms. While direct thermal injury to the lower respiratory tract is theoretically possible, it is exceptionally rare, as the upper airway functions as an efficient heat exchanger, dissipating thermal energy before it reaches the trachea. Consequently, thermal injury is usually limited to the supraglottic airway, manifesting as laryngeal edema and upper airway obstruction.

Injury to the lower respiratory tract is mediated primarily by the chemical byproducts of incomplete combustion, which bypass upper airway defenses and deposit directly in the distal airways and alveoli.

These combustion products directly damage the epithelium, causing necrosis, ciliary dysfunction, and surfactant inactivation. In addition, they stimulate the release of neuropeptides (substance P, neurokinins, and calcitonin gene-related peptide) from activated vagal sensory nerve endings, promoting vasodilatation, increasing microvascular permeability, and recruiting neutrophils to the injury site. The resultant pulmonary edema, together with small airways obstruction from sloughed epithelium and mucus, predisposes to atelectasis, intrapulmonary shunting, and secondary infection.

In recent years, e-cigarette, or vaping product use, associated lung injury (EVALI) has emerged as a contemporary form of toxic inhalation injury. First described in 2019, EVALI manifests with acute respiratory symptoms in individuals with a history of vaping within 90 days of symptom onset, in the absence of identifiable infection. The primary pathogenic agent implicated is vitamin E acetate, a chemical used as a thickening agent in tetrahydrocannabinol (THC) containing vaping products. Bronchoalveolar lavage fluid from patients with suspected EVALI consistently demonstrates the presence of vitamin E acetate, which is absent in healthy comparators. When heated, vitamin E acetate undergoes pyrolysis, generating ketene gas that causes direct epithelial injury to the distal airways and alveoli. Furthermore, vitamin E acetate incorporates into pulmonary surfactant membranes, causing “softening” and impaired biophysical function independent of inflammatory effects. Diagnosis of EVALI remains one of exclusion and requires a high index of clinical suspicion, particularly in younger patients presenting with unexplained respiratory symptoms and a history of vaping.

Infectious Lung Injury

Bacterial pathogens injure the lung through diverse and concurrent mechanisms. Some, like Streptococcus pneumoniae, release pore-forming toxins (e.g. pneumolysin) that directly lyse alveolar epithelial and endothelial cells. Lipopolysaccharide from gram-negative bacteria binds to Toll-like receptors on alveolar macrophages, triggering release of cytokines that activate pulmonary endothelium and recruit neutrophils. Others, such as Pseudomonas aeruginosa degrades elastin and cleaves surfactant through elastases, and disrupts cell membranes by injecting cytotoxic phospholipases directly into host cell cytoplasm. Staphylococcus aureus can produce superantigens (e.g. toxic shock syndrome toxin-1) that bind with high affinity to MHC class II molecules in the absence of antigen processing, stimulating over 20% of all T-cells, leading to cytokine storm.

Viral pathogens, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), cause lung injury through direct cytopathic effects and dysregulated host immune responses. The virus enters alveolar type II cells via spike protein binding to angiotensin-converting enzyme 2 and causes epithelial

necrosis and sloughing. Concurrently, endothelial injury disrupts VE-cadherin junctions, increasing capillary permeability and promoting microvascular thrombosis. The infected epithelial cells and alveolar macrophages release proinflammatory cytokines, and this dysregulated inflammation culminates in acute respiratory distress syndrome (ARDS).

Inflammatory and Immunological Lung Injury

Systemic inflammation from non-pulmonary sepsis, pancreatitis, or major trauma can induce acute lung injury in the absence of direct pulmonary infection, also known as extrapulmonary ARDS. Circulating inflammatory mediators (e.g. endotoxin, TNF-α) activate the pulmonary vascular endothelium, upregulating adhesion molecules such as ICAM-1 and P-selectin. This leads to sequestration and transmigration of primed neutrophils into the interstitium and alveoli, where they release proteases and reactive oxygen species that increase capillary permeability.

Immunologic lung injury involves the adaptive immune system mistakenly damaging lung tissue. Antibodies may directly bind to alveolar basement membranes (e.g. Goodpasture syndrome), activate neutrophils to penetrate vessel walls and release toxic oxygen radicals to damage adjacent alveolar endothelium (e.g. ANCA-associated vasculitis), or form immune complexes that deposit in pulmonary capillaries, triggering inflammation and complement activation (e.g. systemic lupus erythematosus). Clinical manifestations range from insidious dyspnea to life-threatening diffuse alveolar hemorrhage. Diagnosis is supported by detection of specific autoantibodies in serum, interpreted in conjunction with clinical, radiographic, and histological findings.

The expanding use of biologic therapies in solid tumors and selected hematological malignancies has introduced novel mechanisms of pulmonary toxicity. Immune checkpoint inhibitors (e.g. anti-PD-1/PD-L1, anti-CTLA-4) enhance T-cell activity against malignant cells but may precipitate immune-related pneumonitis when over-activated T-cells target antigens expressed in both tumor and healthy lung tissues. Chimeric antigen receptor T-cell therapy involves harvesting a patient’s own T-cells, genetically engineering them to recognize cancerous cells, and re-infusing them into the subject. The resulting T-cell mediated cytotoxicity may be accompanied by cytokine release syndrome, activating endothelial cells, including the pulmonary vasculature, and cause non-cardiogenic pulmonary edema in severe cases.

Drug Induced Lung Injury

Drug-induced lung injury occurs through two primary mechanisms: direct cytotoxic damage and immune-mediated injury, which are often interdependent. Direct cytotoxic injury results from dose-dependent damage to pneumocytes or the alveolar capillary endothelium. This mechanism is exemplified by chemotherapeutic agents like bleomycin, which cause direct cellular damage leading to diffuse alveolar damage (DAD) and potentially acute respiratory distress syndrome.
The cytotoxic pathway can trigger an abnormal wound healing response, with overactivation of inflammatory macrophages releasing reactive oxygen species, proteases, and tumor necrosis factor-α, which exacerbate acute injury and may progress to chronic fibrosis.

Immune-mediated mechanisms involve all types of immunological reactions causing drug-induced interstitial lung disease appears to be T cell-mediated. This pathway is characterized by hypersensitivity reactions where the drug acts as an antigen, triggering granulomatous inflammation similar to hypersensitivity pneumonitis.

The severity of drug-induced lung injury ranges from mild infiltrates to life-threatening respiratory failure, with manifestations including organizing pneumonia, eosinophilic pneumonia, nonspecific interstitial pneumonia, pulmonary hemorrhage, and pulmonary edema.

Ventilation Induced Lung Injury

Invasive mechanical ventilation is a life-saving tool that supports gas exchange and unloads the work of breathing. However, it also imposes physical forces on an already compromised lung. The pressures that recruit collapsed alveoli may overdistend others; tidal volumes that sustain oxygenation can strain fragile tissue; and the cyclic nature of ventilation can generate shear stress at the interfaces between injured and healthy lung units. These forces may amplify the injury sustained from the original insult. Understanding the mechanisms by which ventilation injures the lung is essential to minimizing iatrogenic harm.

Barotrauma

Barotrauma, the first described form of VILI, is defined by alveolar rupture from elevated trans-alveolar pressure, causing air to leak into the extra-alveolar tissue. This escaping air can result in pneumothorax, pneumomediastinum, and subcutaneous emphysema.

Historically, the use of large tidal volumes and pressures was standard care in patients requiring mechanical ventilation. Webb and Tierney conducted the first comprehensive study in 1974, demonstrating that high airway pressures (> 45 cm H_2O) caused perivascular and alveolar edema, establishing the link between alveolar distension and injury.

At the cellular level, stretching the lung beyond its capacity ruptures alveolar cell membranes. This mechanism was elucidated by Macklin et al., who found that alveolar rupture leads to gas escaping along the pulmonary vascular sheaths toward the mediastinum, causing pneumomediastinum, subcutaneous emphysema, and pneumothorax.

Volutrauma

Volutrauma refers to injury induced by overdistension of the lung during mechanical ventilation. Dreyfuss et al. recognized that the main determinant of VILI was excessive strain (change in volume compared to the functional residual capacity), calling attention to volume instead of pressure as the primary driver of injury. They demonstrated that ventilation with large tidal volumes increases alveolar permeability and triggers inflammatory responses, resulting in pulmonary edema. These findings suggested that volume-induced lung stretch was the primary cause of injury, leading to the concept of "volutrauma."
The constraining physical limit of lung structure is achieved at total lung capacity. Damage occurs when applied energy repeatedly distends the lung beyond its limit through 'micro-fractures' of the extracellular matrix, inflammatory signaling, and vascular stresses that lead to tissue wounding and inflammatory activation.

The clinical translation of these principles led to the ARMA trial: limiting tidal volume to 6 ml/kg of ideal body weight and plateau pressure to 30 cm H_2O in patients with ARDS. The results were a significant reduction in mortality (39.8% vs. 31.0%) and ventilator-free days (12 ± 11 days vs. 10 ± 11 days). Since then, this approach has become the standard of care in ARDS management.

Atelectrauma

Atelectrauma occurs in collapsed alveoli when the tidal pressures are sufficient to inflate collapsed alveoli that then collapse again with exhalation. The cyclical recruitment and derecruitment create a shear force that injures the alveolar epithelium, disrupts surfactant function, and triggers a pro-

inflammatory cascade, leading to increased capillary permeability and edema. The weight of the edematous lung further contributes to regional atelectasis, creating a vicious cycle.

Lung injury from atelectrauma is amplified by stress multipliers, a geometrical deformation of neighboring, aerated units that amplifies the stress and strain of a tidal volume (Figure 1). Models developed by Mead et al. showed that pressure at the interface between consolidated and aerated units can be 4–5 times higher than the applied airway pressure, exposing healthy alveoli to injurious stress. This regional interdependence is further complicated by edema. Perlman et al. showed that a fluid-filled alveolus causes the septal wall to bow inward, mandating that the neighboring alveoli over distend and reduce overall compliance by approximately 24%. Furthermore, heterogeneous alveolar flooding results in the cyclic formation and destruction of foam bubbles at the gas-liquid interface, contributing to local interfacial stress, directly disrupting alveolar cells and propagating injury.

A direct link between mechanical heterogeneity of the lung parenchyma and increased mortality in ARDS patients has been confirmed, reinforcing the critical role of regional mechanical stresses in disease progression. The effort to prevent atelectrauma is the foundation of the “open lung” approach of mechanical ventilation. The primary tool to achieve this is the careful titration of positive end-expiratory pressure (PEEP).

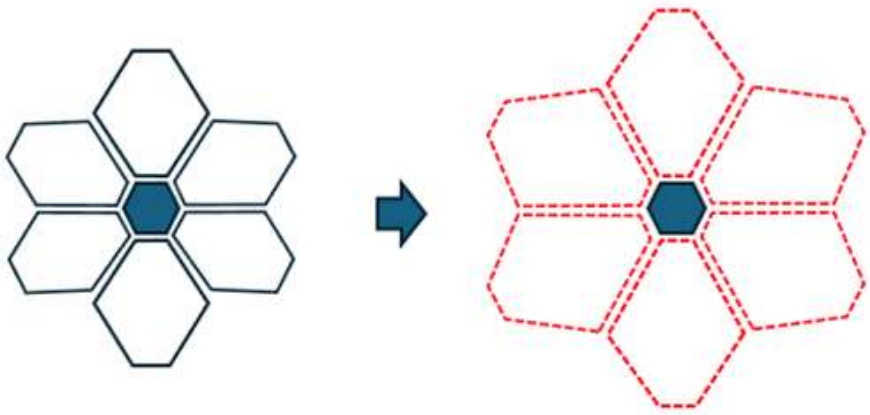

Figure 1: Stress multipliers. Consolidated alveoli cause a geometrical deformation of neighboring, aerated units. Applying a tidal volume amplifies this deformation, increasing the regional alveolar stress and strain.

Biotrauma

Biotrauma refers to the systemic inflammatory response incited by the physical forces of VILI. Both alveolar overdistension and atelectrauma trigger the release of pro-inflammatory mediators including

tumor necrosis factor-alpha, interleukin-6, interleukin-8, matrix metalloproteinase-9, and nuclear factor NF-kB. This cascade can occur within hours of injurious ventilation strategies.

This pro-inflammatory response contributes to extrapulmonary organ dysfunction, increasing the risk of multiorgan failure and death. These effects have been demonstrated in human clinical trials showing that lung-protective ventilation attenuates systemic inflammation and extrapulmonary organ system failures. Furthermore, a sustained inflammatory state may promote pulmonary fibrosis in the recovery phase of ARDS.

Rheological Theory

Rheological theory unifies the concepts of barotrauma and volutrauma by modelling the lung as a viscoelastic body. This paradigm renders the historical debate obsolete by demonstrating that pressure (stress) and volume change (strain) are two manifestations of the same injurious process–the deformation of lung parenchyma.

The relationship is governed by Hooke's law, which states that for an elastic solid, Stress = Ey x Strain, where Ey (Young's modulus) defines the material's stiffness. Gattinoni and Protti established that the respiratory system behaves as such a solid, obeying the equation:

$$\Delta PTP = ESL \times (VT/FRC)$$

In this critical formulation, transpulmonary pressure (ΔPTP) is the stress, the ratio of tidal volume to functional residual capacity (VT/FRC) is the strain, and specific lung elastance (ESL) is the Young's modulus that describes the lung's elasticity. This constant (approximately 13.5 cm H_2O in ARDS) dictates a fixed coupling between stress and strain; a specific strain will generate a proportional stress, and vice versa. The linear relationship between stress and strain is preserved up to a strain value of 1, such that the alveoli will regain their original shape after the inflation forces have been removed. The stress-strain relationship, however, begins losing its linearity between strain values of 1.5 and 2, marking the "elastic limit". Beyond this threshold, the structure fails, and irreversible microfractures begin to occur in the lung parenchyma (Figure 2).

Thus, the rheological model provides a biomechanically grounded and unified explanation of volume and pressure-induced lung injury.

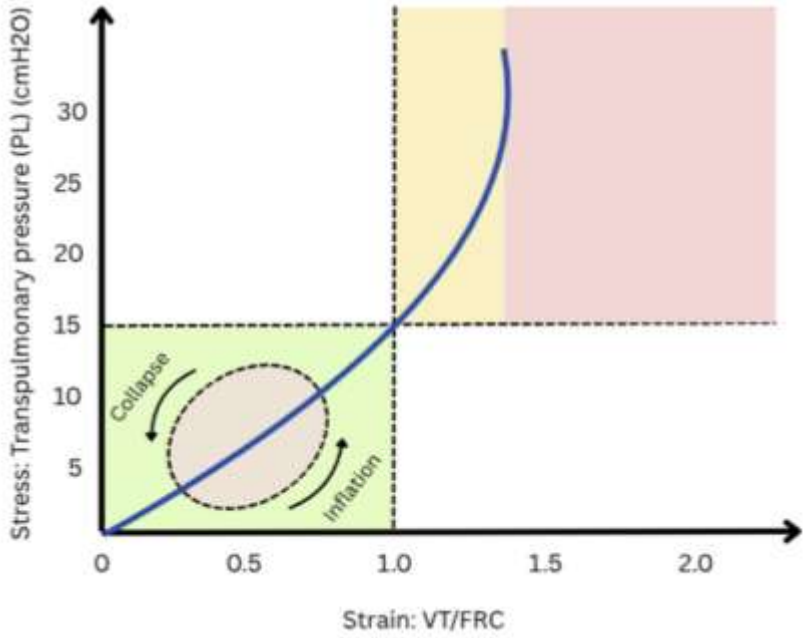

Figure 2: Stress–strain relationship in lung mechanics. The graph plots stress (transpulmonary pressure, PL, cmH_2O) against strain (tidal volume relative to functional residual capacity, VT/FRC) of the lung during inflation. The green shaded area represents the safe zone, where alveoli are recruited and ventilated within physiological limits. The yellow-shaded area corresponds to the risk of overdistension, and the red-shaded area indicates the risk of alveolar injury.

Ergotrauma

While the aforementioned mechanisms collectively contribute to VILI, current ventilation approaches primarily focus on optimizing individual components. In practice, these co-factors play a role in the mortality associated with specific ventilation strategies. To address this, Gattinoni et al. first proposed mechanical power (MP) to unify the total energy delivered per minute (Joules per minute) to the respiratory system during positive pressure ventilation.
Measured in Joules per minute, MP is calculated as:

$$MP = (\Delta V^2 \times [(0.5 \times ERS + RR \times (1 + I{:}\,E)/(60 \times I{:}\,E) \times RAW) + \Delta V \times PEEP]) \times RR$$

where ΔV is the tidal volume, ERS is the elastance of the respiratory system, I: E is the inspiratory-to-expiratory time ratio, and RAW is the airway resistance.

Importantly, not all components of MP contribute equally to its potential for injury. For instance, doubling the respiratory rate increases MP by 1.4-fold, while doubling PEEP increases it by twofold. In contrast, doubling VT has a disproportionately large effect, increasing MP by fourfold. This

highlights that the injurious potential of MP is more closely tied to the elastic energy than the volume change itself.

Clinically, prolonged elevation of mechanical power has been associated with mortality69. In experimental models, MP was positively correlated with neutrophilic inflammation, a hallmark of ARDS70. This is reflected in patient outcomes, with MP exceeding 17 J/min in ARDS and 14 J/min during the first three days of ECMO being linked with increased mortality.

Consequently, limiting MP has emerged as a promising strategy for lung-protective ventilation. By mitigating the cumulative and disruptive energy load on lung tissues over time, this approach aims to reduce the deformation of cells and the extracellular matrix, thereby lowering the risk of VILI.

Patient Self-Inflicted Lung Injury

Patient self-inflicted lung injury (P-SILI) remains a nascent and contested concept. Although animal and preclinical studies have generated compelling hypotheses, definitive studies are still required to delineate the precise pathophysiological mechanisms underlying P-SILI. Current understanding attributes P-SILI to cyclical fluctuations and regional heterogeneity in transpulmonary pressure, driven by excessive patient respiratory effort, whether during unassisted spontaneous breathing or in conjunction with mechanical ventilation (Figure 3).

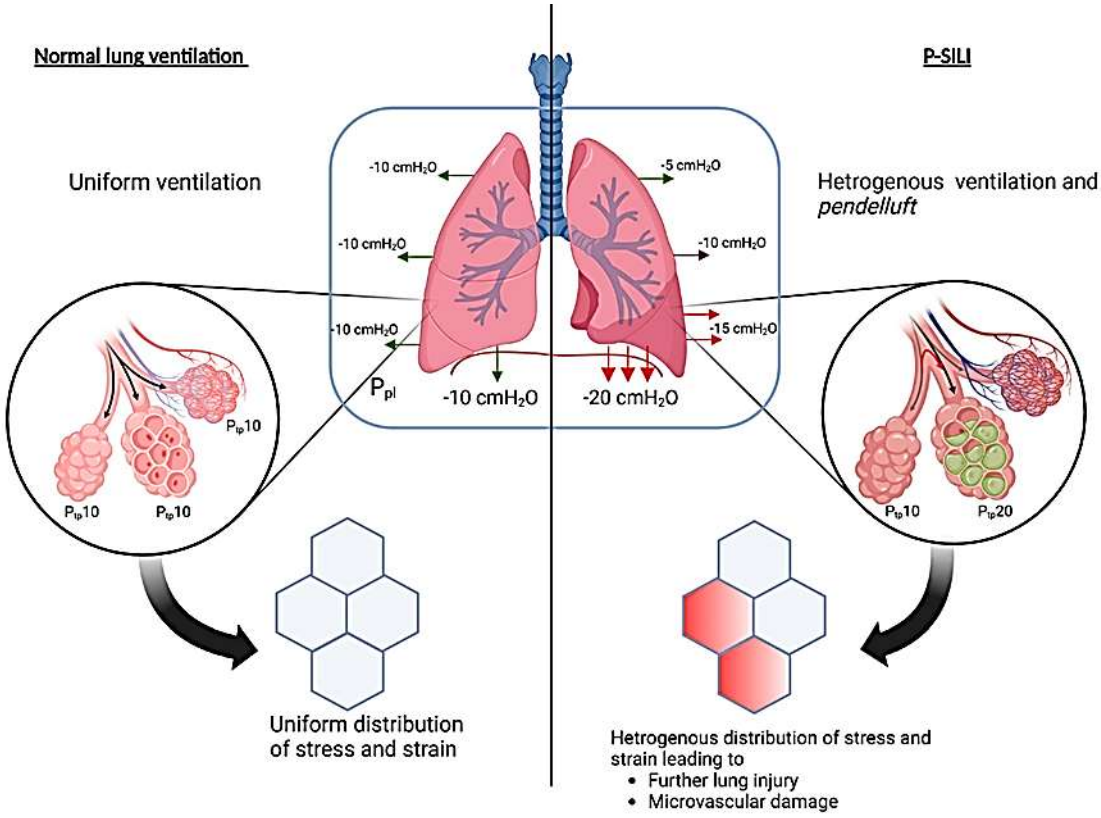

Figure 3: The pathophysiologic mechanism of P-SILI. Reproduced from reference 74 with permission.

The Impact of Excessive Inspiratory Effort on Alveolar Over-Distension

The intensity of neural output from the respiratory centers, known as the respiratory drive, dictates the workload of the respiratory muscles. This drive is shaped by inputs from central and peripheral chemoreceptors, stretch receptors embedded in the thoracic wall and lung parenchyma, irritant receptors in the airway epithelium, as well as cortical influences and emotional feedback.

In pathological states such as ARDS, respiratory drive is amplified by hypoxemia, hypercapnia, and vagal C-fiber activation secondary to inflammation and congestion. These vigorous inspiratory efforts

generate markedly negative pleural pressures, which in turn increase transpulmonary pressure and promote alveolar over-distension, especially in regions of low compliance.

Pendelluft and Regional Heterogeneous Ventilation

Pendelluft, the movement of gas within the lungs from one region to another due to differing time constants, is a key factor in P-SILI. This phenomenon involves the transfer of gas from areas of low time constants to relatively higher time constants during inspiration. A reverse flow can occur during expiration. This gas movement occurs without new gas entering the alveoli, essentially creating a localized form of dead-space ventilation (Figure 4). The resulting uneven distribution of ventilation leads to localized alveolar over-distension and shear stress, particularly at the boundaries between aerated and consolidated lung tissue.

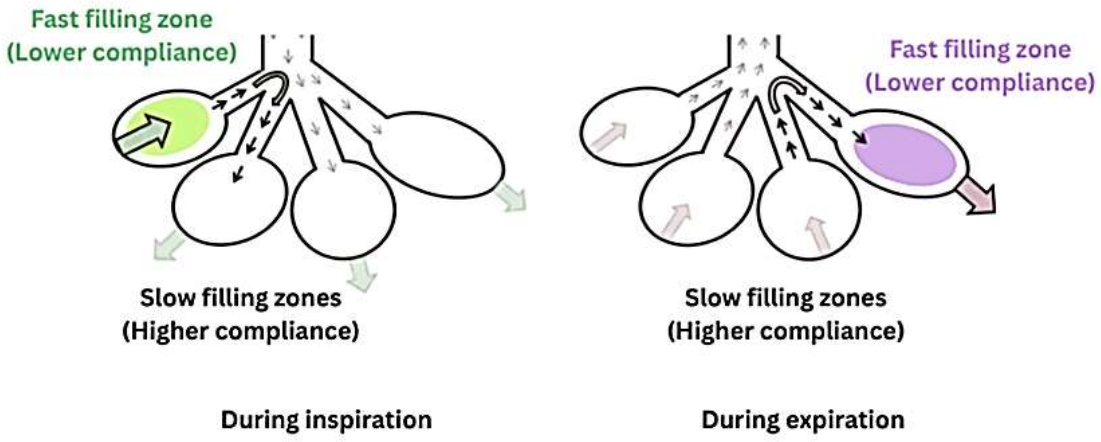

Figure 4: Pendelluft: intrapulmonary gas redistribution

The uneven distribution of pleural pressure in injured lungs further complicates this process. During spontaneous inspiration, a more negative pleural pressure is generated in dependent lung regions compared to non-dependent areas. This pressure difference causes dependent lung regions to inflate preferentially during inspiration, effectively shifting tidal volume away from the non-dependent areas. In patients with significant expiratory effort, the collapse of dependent lung regions during exhalation can intensify pendelluft during the next inspiration (Figure 5). This phenomenon can occur in both spontaneous breathing and during mechanical ventilation, particularly when an uncontrolled inspiratory effort occurs.

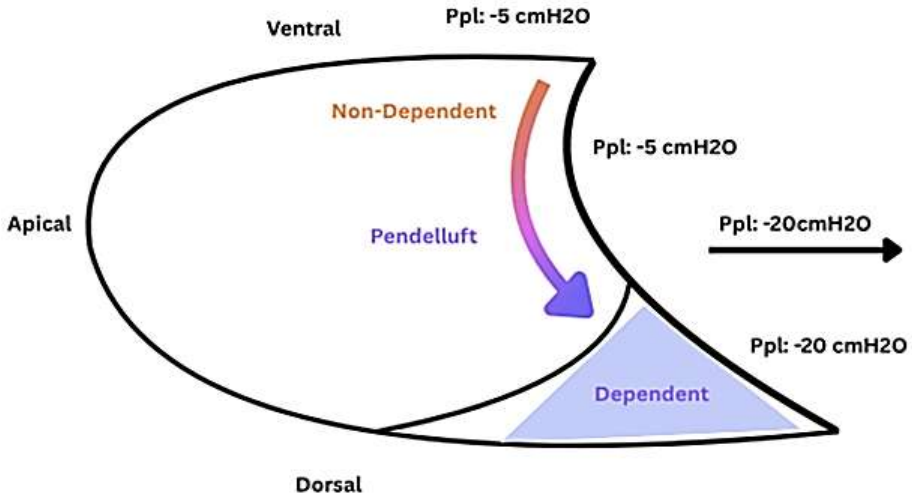

Figure 5: Pendelluft driven by regional pleural pressure gradients. Owing to the stronger contraction of the diaphragm's posterior fibers, inspiratory pleural pressures become more negative in dorsobasal regions than ventrally. In injured lungs, this uneven pressure field drives an intrapulmonary shift of gas from ventral to dorsobasal compartments.

Yoshida et al. demonstrated this using electrical impedance tomography and dynamic computed tomography (CT) in a porcine model of lung injury. Their research showed that spontaneous breathing led to approximately 1.5–2 times greater inflation of dependent lung regions during the early phase of inspiration compared to passive breaths, while simultaneously observing transient deflation in non-dependent regions.

Local Lung Congestion

Kallet et al. described a patient with presumed ARDS whose pulmonary edema acutely worsened after instituting a low-tidal-volume, lung-protective ventilation strategy in the presence of spontaneous breathing efforts. Using a lung-model simulation and direct measurements, they showed that vigorous inspiratory efforts generated considerable negative intrathoracic pressures, elevated the trans-vascular pressure gradient, and produced an edema fluid/plasma protein ratio (~0.47) consistent with hydrostatic pulmonary edema.

Vigorous inspiratory efforts generate substantial negative intra-thoracic pressures, thereby increasing venous return, elevating left ventricular end-diastolic pressure, and increasing pulmonary capillary pressures. This creates an augmented trans-capillary pressure gradient. Given the pre-existing increase in capillary permeability secondary to endothelial dysfunction in acute lung injury, this elevated gradient facilitates fluid extravasation from the pulmonary capillaries into the interstitial and alveolar

spaces, ultimately leading to pulmonary edema. The edema exacerbates hypoxemia and hypercarbia, and directly stimulates vagal C-fibers, further augmenting respiratory effort.

Spontaneous Breathing Effort During Mechanical Ventilation

Patient-ventilator dyssynchrony occurs when a patient's own breathing efforts fall out of sync with the ventilator's cycles. It is known to intensify the work of breathing and augment transpulmonary pressures, contributing to excessive lung stress and strain. The precise ways in which different dyssynchrony patterns promote lung injury, and how strongly each pattern drives P-SILI, are not yet fully defined.

Pohlman et al. found that double-triggered breaths significantly increased delivered tidal volume, averaging 10.1 ml/kg of predicted body weight compared to 5.9 ml/kg PBW for synchronous breaths. Similarly, Beitler observed in 33 ARDS patients receiving low-tidal-volume ventilation that double-triggered breaths resulted in tidal volumes of 11.3 ml/kg PBW. Sottile et al. further demonstrated that double-triggered and flow-limited breaths in ARDS patients, or those at risk, were associated with larger-than-expected tidal volumes during low-tidal-volume ventilation. Moreover, these dyssynchronous breaths delivered large tidal volumes (>10 mL/kg) much more frequently (47%–61%) than synchronous breaths (0.9%). A unique aspect of this study was that most patients were on a dual-triggered ventilation mode, where variable patient effort could lead to differing delivered tidal volumes, explaining why even flow-limited breaths could result in excessive volumes.

Beyond excessive tidal volumes, dyssynchrony amplifies lung stress through altered transpulmonary pressures. Under complete ventilator control, plateau pressure serves as a surrogate for transpulmonary pressure. However, when a patient generates strong negative pleural pressures, transpulmonary pressure can surge significantly above the recorded plateau pressure, thereby increasing the risk of barotrauma. In animal models, spontaneous efforts during both volume- and pressure-controlled modes drove transpulmonary pressures above 33 cm H_2O, despite "safe" plateau pressures below 30 cm H_2O, resulted in worse lung injury on pathology. These data imply that vigorous patient effort during dyssynchrony may generate high regional stresses and exacerbate injury, particularly in lungs already compromised by disease.

Consequences of VILI and P-SILI

Ventilator-induced lung injury (VILI) and patient self-inflicted lung injury (P-SILI) promote a self-perpetuating cycle of lung injury that escalates to systemic organ dysfunction. The consequences extend far beyond the lung, determining both short-term survival and long-term recovery.

Progressive Pulmonary Dysfunction

The initial mechanical and biological insults create a state of progressive pulmonary dysfunction. Alveolar edema, atelectasis, and surfactant loss combine to create ventilation-perfusion (V/Q) mismatch and intra-pulmonary shunting, resulting in refractory hypoxemia and hypercapnia. This inefficiency in gas exchange necessitates a fundamental shift in ventilation strategy: the acceptance of permissive hypercapnia to prioritize lung protection over normalization of blood gases.

Concurrently, the accumulation of edema and inflammatory infiltrates reduces pulmonary compliance, mandating higher airway pressures to achieve a given tidal volume and increases the patient's work of breathing. In the case of P-SILI, the heightened work triggers strong inspiratory efforts, elevating transpulmonary and trans-vascular gradients, thereby exacerbating the original injury. Furthermore, these insults also trigger a biological inflammatory response (biotrauma), which amplifies lung damage and worsens pulmonary dysfunction.

Diaphragmatic Dysfunction

Diaphragm dysfunction arises through three principal mechanisms: disuse atrophy from sedation and excessive ventilatory assistance; concentric load–induced injury when the diaphragm over-contracts against insufficient support; and eccentric load–induced injury during expiratory contractions.

Prolonged sedation and excessive ventilatory assistance unloads the diaphragm, precipitating rapid disuse atrophy. Animal models demonstrate that controlled mechanical ventilation reduces diaphragm fiber cross-sectional area by over 20 percent within 12 hours and decreases overall muscle mass by 48 hours, accompanied by mitochondrial dysfunction, oxidative stress, and upregulated proteolytic signaling pathways. Conversely, when ventilatory support is insufficient, excessive inspiratory drive exposes the diaphragm to injurious loads and strain, leading to concentric myotrauma.

Eccentric myotrauma occurs when the diaphragm is actively lengthening while contracting, typically during the expiratory phase of various patient-ventilator asynchronies, such as premature cycling,

reverse triggering, or ineffective efforts. Preclinical evidence suggests that these post-inspiratory loading events induce injurious shear stresses, resulting in a rapid loss of force-generating capacity and structural damage. The clinical challenge is compounded by the difficulty in detecting these asynchronies, suggesting the true incidence of eccentric myotrauma is likely underappreciated.

The combination of worsening lung mechanics and diaphragmatic weakness hinders the patient's ability to liberate from the ventilator, prolonging weaning, rehabilitation, and increasing exposure to associated complications.

Systemic Organ Failure

The most critical consequence of VILI and P-SILI is the propagation of injury beyond the lungs, leading to multi-organ failure and driving mortality. Ventilator-induced biotrauma unleashes a systemic inflammatory cascade by disrupting the alveolar–capillary barrier and activating both epithelial and endothelial cells. Mechanical overdistension and cyclic collapse trigger the local release of proinflammatory mediators, such as interleukin-1β, interleukin-6, tumor necrosis factor-α, and upregulate adhesion molecules on the endothelium, facilitating leukocyte recruitment and capillary leak. Once in the bloodstream, these cytokines drive endothelial activation in distant vascular beds, precipitating a sepsis-like systemic inflammatory response syndrome and multi-organ dysfunction.

P-SILI follows a parallel biotraumatic pathway. Excessive negative pleural pressures and large regional strains caused by vigorous spontaneous efforts disrupt the same alveolar–capillary interface, provoking local cytokine release. In experimental models of P-SILI, intense unassisted breathing in injured lungs markedly elevates plasma IL-6 and TNF-α compared with passively ventilated controls, and these circulating mediators correlate with early signs of extrapulmonary organ inflammation.

Strategies to Mitigate Ventilator-Induced Lung Injury (VILI)

Limiting Tidal Volume and Driving Pressure

ARDS was once thought to be a homogenous disease, necessitating high tidal volumes and pressures to normalize gas exchange101. With the advent of computed tomography (CT), it was recognized that ARDS lungs are, in fact, heterogeneous, with densities preferentially distributed in the dependent regions and relative sparing of the non-dependent areas. This finding gave rise to the concept of the "baby lung": a lung that is smaller, not stiff. This provided the rationale for the landmark ARDSnet ARMA trial, which compared a high-stretch (12 ml/kg of predicted body weight [PBW]) to a low-stretch (6 ml/kg of PBW) tidal volume ventilation strategy, and demonstrated a significant reduction in mortality with the latter30. Despite being conducted over two decades ago, this practice remains the mainstay of mitigating VILI and is strongly recommended in the latest ESICM and ATS guidelines.

While normalizing tidal volume to PBW accounts for the anatomical lung size, it fails to consider the functional lung size (aka "baby lung") available for ventilation in ARDS. As respiratory system compliance is directly related to the volume of aerated lung, the impact of a given VT is better assessed when normalized to compliance (CRS)a ratio also known as driving pressure ($\Delta P = VT / CRS$). A retrospective analysis of previous RCT data demonstrated that driving pressure was the ventilator variable most consistently associated with survival, independent of PEEP and plateau pressure. More recently, a secondary analysis of five RCTs revealed that the mortality benefit of lower tidal volume varies according to respiratory system elastance, further suggesting that driving pressure should be the primary target in lung-protective strategies. Nevertheless, the use of driving pressure as a primary target has yet to be validated in a dedicated, high-quality RCT, and its benefit remains speculative.

PEEP Titration

Titrating PEEP is central to the "open lung" approach, balancing the prevention of atelectrauma against alveolar overdistension. The optimal method of setting PEEP, however, remains elusive.

The PEEP/FiO_2 table from the ARDSnet protocol remains the most widely recognized titration algorithm. Two versions exist: a lower-PEEP strategy, which applies the minimum PEEP required for acceptable oxygen levels, and a higher-PEEP strategy, which aims to recruit and stabilize lung units.

As three major RCTs have not demonstrated a clear mortality benefit for either approach, current guideline recommendations remain divergent.

Building on the understanding that PEEP has dual and opposing effects in the heterogeneous ARDS lung, the “best compliance” strategy offers a physiological and practical bedside approach to PEEP titration. This method posits that the PEEP level that yields the highest respiratory system compliance identifies the equilibrium point between alveolar recruitment and overdistension. However, the accuracy of this measurement can be compromised by several confounders. A primary concern is intra-tidal recruitment, where the cyclical opening of collapsed alveoli during tidal ventilation artificially elevates compliance, creating a false impression of improved lung mechanics. A recent study in patients with COVID-19 ARDS demonstrated that intra-tidal recruitment rather than reduced overdistension accounted for the observed increase in compliance during a decremental PEEP trial in nearly half of cases. A second confounder is airway closure, a phenomenon reported in up to 40% of ARDS patients110. In these patients, lung inflation commences when airway pressure surpasses the airway opening pressure (AOP). The clinical importance of this is that when PEEP is set below the AOP, the measured driving pressure is artificially high, leading to an underestimation of the respiratory system compliance. Finally, the “best compliance” approach assumes that the effects of recruitment and overdistension have opposite yet symmetrical impacts on lung compliance. However, compliance is a global measure and cannot discern regional heterogeneity. A recent animal model study highlighted this limitation, demonstrating that changes in global compliance correlated with alterations in dorsal lung regions, but not in the ventral regions. Therefore, the “best compliance” approach should not be viewed as a definitive solution, but rather as one data point to be integrated with other clinical parameters.

Measuring the pleural pressure with an esophageal balloon allows for the partitioning of respiratory mechanics by distinguishing the pressure effects on the lung from those on the chest wall. As the transmural pressure dictates alveolar volume, setting PEEP to maintain a positive end-expiratory transpulmonary pressure targets the prevention of atelectasis and promotion of lung recruitment. A pilot RCT testing this approach showed significantly improved oxygenation, compliance, and a trend toward lower 28-day mortality compared to a standard low PEEP/FiO_2 table. However, a follow-up multicenter trial, powered for clinical outcomes, failed to confirm these benefits. A post-hoc analysis suggested a potential benefit in patients with severe ARDS without multiorgan injury, but this remains speculative and requires further validation. Furthermore, the technique demands precise insertion,

positioning, volume filling, and data interpretation by trained personnel, which currently restricts its use primarily to research settings.

Electrical impedance tomography (EIT) is a non-invasive, bedside imaging technique that reconstructs internal electrical conductivities to display real-time regional ventilation distribution. By quantifying the change in compliance at a pixel level, EIT can compute the overall modifiable lung collapse and overdistension during a decremental PEEP trial. Assuming both collapse and overdistension are equally deleterious, setting PEEP at the "crossing point" aims to minimize both conditions simultaneously. While animal studies have demonstrated physiological benefits with this approach, its efficacy and impact on clinical outcomes remain to be validated in human trials.

Recruitment maneuvers

In severe ARDS, up to 40% of the lung can remain non-aerated despite plateau pressures being limited to 30 cm H_2O. As part of the "open lung" approach, recruitment maneuvers (RM) temporarily elevate airway pressures beyond this limit to re-aerate collapsed units, thereby attenuating VILI by increasing the size of the "baby lung" and reducing alveolar stress and strain. However, RM also carries risks of alveolar overdistension and hemodynamic instability. Two fundamental components determine the success of RM: individualization and duration.

The landmark study by Cavalcanti et al. was the first to evaluate RM in a large multicenter RCT, building on earlier evidence of their physiological benefits. The trial compared a protocol that included routine RM to a low PEEP/FiO_2 strategy in patients with moderate-to-severe ARDS and found significantly higher mortality in the intervention group. Another trial that personalized ventilation strategy to lung morphology (using low PEEP and prone positioning in focal ARDS versus high PEEP and RM in non-focal ARDS) found no overall mortality difference compared to a low PEEP/FiO_2 strategy. However, a subgroup analysis identified increased mortality when the ventilation strategy was misaligned with the underlying lung morphology.

A key insight from this collective evidence is that the benefit of RM is highly dependent on the individual patient's physiological phenotype. When applied to patients with a recruitable lung, RM may improve outcomes; conversely, they can be detrimental in those with non-recruitable lungs131,132. This understanding has established the principle of assessing the potential for recruitability before performing an RM. Although CT is the gold standard for assessing recruitability,

two bedside-accessible recruitability assessment indices are available, offering a practical means to personalize RM in the clinical setting.

The duration of sustained high pressure is another critical determinant of RM success, as hemodynamic instability is the primary reason for interruption. The physiology underlying this is twofold. First, given the short time constant of consolidated alveoli, the majority of recruitment occurs within the first 10 seconds; extending the maneuver beyond this point provides no further benefit to oxygenation. Second, hemodynamic impairment typically manifests after the tenth second. The mechanism involves an immediate decrease in right ventricular preload due to high intrathoracic pressure. However, arterial hypotension becomes apparent only after a few cardiac cycles, reflecting the time needed for this reduced preload to transit the pulmonary circulation and impair left ventricular output. Nevertheless, current guidelines recommend against the use of prolonged RM, defined as sustained airway pressures above 35 cm H_2O for more than one minute (as used in Cavalcanti's trial), given their association with harm. Conversely, trials that used brief RM, defined as sustained airway pressures above 35 cm H_2O for less than one minute, have not shown detriment but are not suggested for routine use. Therefore, future research trials should investigate whether brief RM in those with a high potential for recruitment can improve patient-centered outcomes.

Prone Positioning

Prone positioning (PP) mitigates VILI through three mechanisms that fundamentally reorganize lung mechanics. First, by reorienting the heavy, consolidated dorsal lung to a non-dependent position, the redistribution of the hydrostatic gradient recruits collapsed alveoli, directly reducing intrapulmonary shunting. Second, the more compliant "baby lung" is shifted to a dependent position, where expansion is limited by the increased chest wall elastance, mitigating overdistension by reducing regional transpulmonary pressure. Third, it homogenizes the pleural pressure gradient. By reducing the ventral-to-dorsal pressure difference, PP creates a more uniform distribution of ventilation, directly attenuating the heterogeneous alveolar stress and strain that are the primary drivers of VILI.

The landmark PROSEVA trial stands alone in demonstrating a survival benefit for PP in moderate-to-severe ARDS, a success attributed to its prolonged session duration (≥16 hours) compared to earlier, negative trials using shorter sessions. Furthermore, post-hoc analyses revealed that "prone responders" (those with improved PaO2/FiO2 ratio) had the same outcome as "prone non-responders". This demonstrates that the survival benefit is not mediated by the reversal of hypoxemia, but by the cumulative protective effect of attenuated VILI.

Consequently, guidelines strongly recommend initiating PP in patients with moderate to severe ARDS with a PaO_2/FiO_2 ratio of < 150 mmHg, despite optimization of ventilator settings. However, PP remains underutilized worldwide. The maneuver is highly complex, labor-intensive, and requires a dedicated team to prevent complications such as tube dislodgement and pressure injuries. Emerging strategies like sequential lateral positioning offer a less labor-intensive, mechanically analogous alternative that may improve practical implementation.

Neuromuscular Blockade and Sedation

Neuromuscular blockade (NMB) and deep sedation are adjunctive therapies in ARDS to facilitate lung-protective ventilatory strategies and minimize VILI. Both target two primary injurious processes: vigorous spontaneous effort (P-SILI) and patient-ventilator dyssynchrony, with a secondary benefit of reducing the work of breathing and its metabolic cost (biotrauma).

The evidence for this strategy, however, is divided by an evolution in ICU practice. The landmark ACURASYS trial, conducted when deep sedation was routine, demonstrated that a 48-hour infusion of Cisatracurium improved survival in moderate-to-severe ARDS. In contrast, the modern ROSE trial found no benefit from NMB and deep sedation when compared to a control group managed with lighter sedation targets and preserved spontaneous efforts. The discrepancy is not a contradiction but a reflection of the evolving standard of ventilation strategies: the ROSE era incorporated more prone positioning and higher PEEP strategies both of which mitigate VILI and received lighter sedation, which reduces diaphragmatic weakness. Together, these advances negate the benefit of routine deep sedation and paralytics.

The conflicting evidence is reflected in divergent guideline recommendations. A synthesized approach, consistent with the ROSE trial and modern sedation practice, would be to initiate ventilation with light sedation. Deep sedation with NMB is then reserved for rescue therapy in patients who exhibit signs of injurious spontaneous efforts or refractory asynchrony, representing the phenotype most likely to benefit, as suggested by the ACURASYS trial.

Extracorporeal Life Support with Ultra-Protective Ventilation

Veno-venous extracorporeal membrane oxygenation (VV-ECMO) represents the ultimate therapy for lung-protective ventilation. By draining deoxygenated venous blood via a central large vein, oxygenating and CO_2 removal through a gas exchange device, and returning it via a second venous cannula, it enables ultra-protective ventilatory strategies (tidal volumes < 4 ml/kg) to minimize the mechanical stress on the injured lung.

The use of VV-ECMO in severe ARDS was studied in two major trials, the CESAR and EOLIA trials. The inclusion criteria for the EOLIA trial now serve as the benchmark for initiation: a PaO_2/FiO_2 < 50 mmHg for > 3 hours, or a PaO_2/FiO_2 of < 80 mmHg for > 6 hours, or a pH of < 7.25 with a $PaCO_2$ of ≥ 60 mmHg for > 6 hours, despite optimizing ventilator settings. A meta-analysis of these trials demonstrated a significant reduction in mortality. Currently, guidelines recommend transferring eligible patients with severe ARDS to an expert ECMO center for evaluation.

Conclusion

Over the past two decades, our understanding of lung injury has evolved from isolated concepts of pressure and volume to a unified model of stress, strain, mechanical power, P-SILI, and diaphragm dysfunction, precipitating a paradigm shift in clinical practice. Lung protective strategies now require not only limiting the global energy delivered (by targeting driving pressure and mechanical power), but also the strategic use of adjuncts such as PEEP, prone positioning, and sedation to homogenize lung stress distribution and modulate respiratory drive. The path forward lies in leveraging advanced monitoring tools to personalize this balance, shifting from population-based thresholds to the management of individualized patient phenotypes.

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