

REVIEW

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Effects of mechanical ventilation on the interstitial extracellular matrix in healthy lungs and lungs affected by acute respiratory distress syndrome: a narrative review

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Abstract

Background Mechanical ventilation, a lifesaving intervention in critical care, can lead to damage in the extracellular matrix (ECM), triggering inflammation and ventilator-induced lung injury (VILI), particularly in conditions such as acute respiratory distress syndrome (ARDS). This review discusses the detailed structure of the ECM in healthy and ARDS-affected lungs under mechanical ventilation, aiming to bridge the gap between experimental insights and clinical practice by offering a thorough understanding of lung ECM organization and the dynamics of its alteration during mechanical ventilation.

Main text Focusing on the clinical implications, we explore the potential of precise interventions targeting the ECM and cellular signaling pathways to mitigate lung damage, reduce inflammation, and ultimately improve outcomes for critically ill patients. By analyzing a range of experimental studies and clinical papers, particular attention is paid to the roles of matrix metalloproteinases (MMPs), integrins, and other molecules in ECM damage and VILI. This synthesis not only sheds light on the structural changes induced by mechanical stress but also underscores the importance of cellular responses such as inflammation, fibrosis, and excessive activation of MMPs.

Conclusions This review emphasizes the significance of mechanical cues transduced by integrins and their impact on cellular behavior during ventilation, offering insights into the complex interactions between mechanical ventilation, ECM damage, and cellular signaling. By understanding these mechanisms, healthcare professionals in critical care can anticipate the consequences of mechanical ventilation and use targeted strategies to prevent or minimize ECM damage, ultimately leading to better patient management and outcomes in critical care settings.

Key points

Question: How does mechanical ventilation affect the lung's interstitial extracellular matrix (ECM), with a specific focus on ECM organization in healthy lungs and those affected by acute respiratory distress syndrome (ARDS).

Findings: The narrative review reveals that mechanical ventilation induces stress on the interstitial ECM, leading to inflammation, fibrogenesis, elastogenesis, and matrix metalloproteinase hyperactivity. Matrix metalloproteinase

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and integrin involvement in ECM damage are emphasized. Our findings are based on a narrative review of studies of mechanical ventilation-induced alterations of interstitial ECM organization and cellular response.

Meaning: The key conclusion is that understanding the intricate processes of interstitial ECM damage, as well as cell signaling and communication related to ventilation-induced lung injury, can pave the way for more targeted interventions that have the potential to mitigate lung damage and improve outcomes for patients in critical care settings.

Keywords Ventilator-induced lung injury, Extracellular matrix, Mechanical ventilation, Collagen fiber, Acute respiratory distress syndrome

Background

The extracellular matrix (ECM) is an intricate structure composed of proteins, polysaccharides, and various other components that envelop and give structure to cells [1]. The primary elements of the ECM include collagen, elastin, proteoglycans, glycosaminoglycans (GAGs), and fibrinogen, which establish the fundamental architecture of bodily tissues. These constituents offer mechanical strength and flexibility, helping to maintain normal fluid dynamics within tissues, providing an efficient low-resistance channel for gas-exchange, regulating cellular activities through the binding of growth factors, chemokines, cytokines, and interactions with cell-surface receptors, and facilitating tissue repair and remodeling [1].

Mechanical ventilation, although lifesaving, can induce excessive stress and strain due to alveolar collapse and overdistension, leading to inflammation, fibrogenesis, elastogenesis, and matrix metalloproteinase hyperactivity, followed by ventilator-induced lung injury (VILI) [2]. VILI has potential to exacerbate respiratory distress, delay healing, and compromise patient outcomes [3]. As the complex interplay of physiologic processes unfolds within the intricate landscape of the respiratory system, the role of the ECM emerges as a crucial determinant in the genesis of VILI [2]. Thus, the influence of the ECM extends beyond its conventional supportive role, extending to mechanotransduction and inflammatory modulation [4]. Under high mechanical stress, ECM components change, which, in turn, affects the delicate balance between tissue stiffness and flexibility, potentiating the propagation of VILI [5, 6]. Understanding of the mechanical stress imparted by mechanical ventilation is essential to comprehend the involvement of the interstitial ECM in the pathophysiology of VILI [4, 7].

Cellular signaling amplifies the significance of the ECM in the genesis of VILI. Integrins, transmembrane receptors that facilitate cell–ECM adhesion, act as intermediaries in mechanochemical communication [8]. In response to mechanical cues generated during mechanical ventilation, integrins transduce signals that regulate processes ranging from cell survival to inflammation [9]. The composition and spatial organization of the ECM influence integrin-mediated signaling, thereby

contributing to the intricate orchestration of inflammatory responses and tissue repair [10].

The interstitial ECM, which is the focus of this review, is found within the spaces surrounding lung cells and fibroblasts, encompassing a network of fibers (e.g., collagen and elastic fibers) [11]. This matrix is crucial for maintaining the structural integrity of the lung, ensuring appropriate mechanical properties for gas-exchange, and mediating cellular responses to mechanical stress [12]. In contrast, the intraluminal ECM, located within the luminal spaces of the lung, including airways and alveoli, primarily interacts with the air we breathe and can be influenced by factors such as inhaled particles and pathogens [13, 14]. Mechanical ventilation imposes mechanical stress that predominantly affects the interstitial ECM, leading to alterations in its composition and organization [15]. While several studies have investigated ECM alterations in the context of mechanical ventilation, distinguishing between changes in the interstitial and intraluminal compartments remains challenging [16]. Most biomarker studies, for example, cannot differentiate between shedding or remodeling of ECM components originating from these distinct compartments [17].

We present a comprehensive review of the interstitial ECM organization in the lungs, mechanisms of mechanotransduction, and ECM modifications during mechanical ventilation in healthy lungs and lungs affected by acute respiratory distress syndrome (ARDS).

Extracellular matrix organization

Lung interstitial ECM consists of basement membranes beneath the cellular epithelium and endothelium, and interstitial spaces containing fibroblasts [11]. The ECM interacts with cells to guide their development and serves multiple functions to preserve cellular homeostasis, including support, tissue segregation, receptor regulation, and pH stabilization [18, 19].

The ECM is composed of macromolecules (Fig. 1): 1. Glycoproteins, including fibronectin, play a crucial role in wound healing, clot formation and ECM assembly [19–22]; 2. GAGs, including sulfated GAGs (heparan sulfate, chondroitin sulfate, dermatan sulfate, and keratan sulfate) [23], are expressed on the cell surface [24]

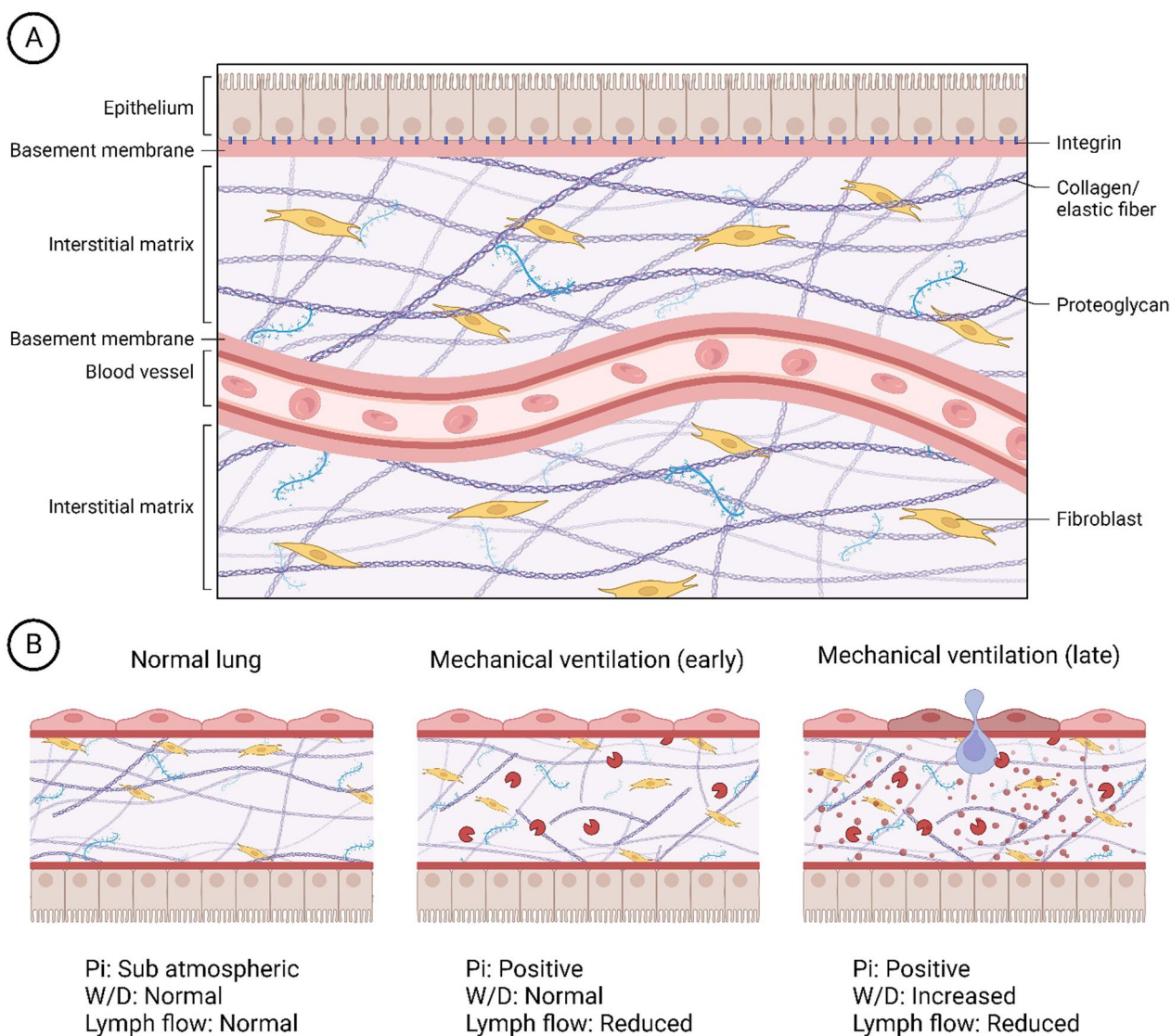


Fig. 1 **A** Normal organization of the extracellular matrix. **B** Changes in the extracellular matrix occur during mechanical ventilation in both early and late phases. Key indicators include interstitial pressure (Pi), the wet-to-dry ratio (W/D), chondroitin sulfate, heparan sulfate, and proteoglycan. Matrix metalloproteinases (MMPs) also play a role. In the initial stages of mechanical ventilation, there is a predominant occurrence of glycosaminoglycan shedding and proteoglycan fragmentation, initiating the inflammatory process and activating MMPs. Subsequently, damage to the alveolar capillary membrane, collagen deposition, and the development of alveolar and interstitial edema occur, ultimately leading to acute respiratory distress syndrome. Figure generated by BioRender

and interact with many proteins [e.g., interleukin (IL)-8 [25], and lipid-binding proteins [26]]. Hyaluronic acid, the most abundant and the largest non-sulfated GAG, is involved in tissue repair, hydration, and protection against infections [27]; 3. Proteoglycans (PGs), including chondroitin sulfate-containing proteoglycans (CS-PG; versican), heparan sulfate proteoglycans (HS-PG; perlecan and glypican), chondroitin and heparan sulfate-containing PGs (CS-HS-PGs; syndecan), and dermatan sulfate-containing PGs (DS-PG; decorin) [28], contain

at least one GAG in their structure, which shares a covalent bond with a core protein [29]. Versican is localized in the lung interstitium, perlecan in the vascular basement membrane, decorin in the interstitium and epithelial basement membrane, and syndecan and glypican in the cell surface. They serve several functions during wound healing and help modulate lung inflammation and remodeling [30]; and 4. Fibrous proteins include fibrillar (types I, II, and III) and non-fibrillar or amorphous collagens (types IV, V, VI) [25, 26]. Elastic fibers provide

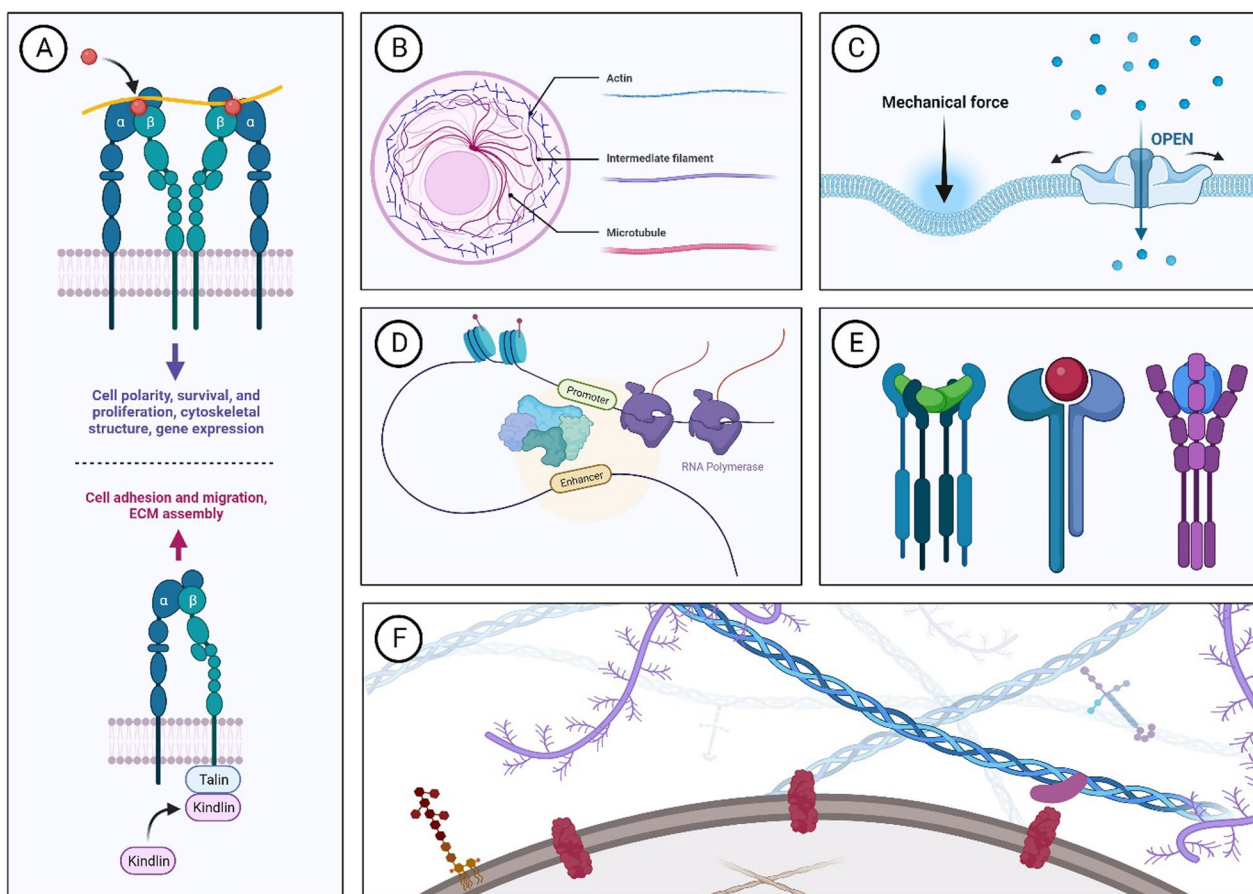


Fig. 2 Key mechanisms involved in mechanotransduction within the extracellular matrix (ECM) include: **A** integrins and focal adhesions; **B** cytoskeletal tension; **C** mechanosensitive ion channels; **D** nuclear deformation and gene expression; **E** soluble factors and paracrine signaling; **F** extracellular matrix remodeling and matrix stiffness and topography. Figure generated by BioRender

elasticity and are abundant in the sub epithelium of alveolar septa [31].

The ECM undergoes dynamic processes of synthesis and breakdown influenced by multiple proteins and enzymes. In this line, matrix metalloproteinases (MMPs) are the most prominent and can lead to GAG shedding, thus causing lung injury [1]. MMP proteolytic activity is tightly regulated by the tissue inhibitors of metalloproteinases (TIMPs) [32, 33]. The distinction between MMP activity in the interstitial versus intraluminal ECM is not well-defined [34].

Mechanotransduction mechanisms

Mechanotransduction refers to the process by which cells convert mechanical stimuli from their environment into biochemical signals [35]. Figure 2 shows the key mechanisms involved in mechanotransduction within the ECM including: 1) Integrins and focal adhesions. When mechanical stress is applied, integrins cluster together and recruit a variety of intracellular

proteins to form focal adhesions [36, 37]; 2) Cytoskeletal tension. The cytoskeleton, a network of fibers within the cell that maintains shape and facilitates movement, consists mainly of actin filaments, microtubules, and intermediate filaments [38]. Mechanical forces can cause the cytoskeleton to either stretch or contract, leading to changes in cell tension, which can activate signaling pathways that regulate cell function [39]; 3) Mechanosensitive ion channels. Mechanosensitive ion channels are a diverse group of transmembrane proteins that can open or close in response to mechanical forces [40]. They can be categorized into two groups based on their activation mechanism [41]. In direct mechanogating, the ion channel is mechanically deformed or stretched by external forces, leading to a conformational change that opens the channel pore [42]. In indirect mechanogating, the ion channel is activated by secondary messengers or cytoskeletal elements that are themselves affected by mechanical forces [43]. Several families of mechanosensitive

ion channels have been identified, including the Piezo channels, a class of ion channels that are critically involved in mechanotransduction [44–46]. In the lungs, Piezo2 help detect and respond to changes in lung stretch, which is essential for maintaining proper lung function and protecting against VILI [47]. Moreover, Transient Receptor Potential (TRP) channels [48] respond to mechanical forces and changes in pH levels, broadening their role in sensory and physiologic processes [49]. The K2P (Two-Pore Domain Potassium) channels are sensitive to various physiologic stimuli, including pH changes, mechanical stretch, temperature, and various pharmacological agents [50]. The mechanosensitivity of certain K2P channels, such as TREK-1, suggests a potential link between these channels and the development of VILI [50, 51]. Furthermore, K2P channel activity could affect the secretion of inflammatory mediators, the recruitment of immune cells to the lung, and the regulation of vascular tone, all of which are relevant in the context of VILI [52]; 4) Nuclear deformation and gene expression. Mechanical forces can be transmitted to the nucleus, leading to changes in its shape and structure [53], which can influence gene expression by altering the physical organization of chromatin and the accessibility of transcription factors to DNA [54, 55]; 5) Soluble factors and paracrine signaling. Mechanical stress can lead to the release of growth factors, cytokines, and other signaling molecules that can diffuse through the ECM and influence the behavior of nearby cells [56]. 6) Extracellular matrix remodeling. Mechanical forces can remodel the ECM by secreting MMPs that degrade ECM components [57]. Remodeling can also involve the synthesis of new ECM proteins with the potential to alter its mechanical properties and affect neighboring cells [58]. 7) Matrix stiffness and topography. ECM stiffness directly influences cellular responses [59]. This stiffness varies across tissues and changes dynamically during disease development, progression, and healing [5]. Cells sense this stiffness through focal adhesions, which connect the ECM to the cell's cytoskeleton via transmembrane proteins (e.g. integrins) [36]. The ECM's topographic features (geometry, orientation, and texture) influence cell alignment, shape, and function [60]. The surface roughness and patterning of the ECM can also affect cell motility, sensing capabilities, and the development of cellular structures [61]. The translation of mechanical cues from ECM stiffness and topography into cellular actions occurs through mechanotransduction pathways [62], which modulate gene expression, cell cycle progression, and apoptosis, tailoring cellular responses to the mechanical environment [63].

Effects of mechanical ventilation on the ECM in healthy lungs

The main mechanisms of VILI, barotrauma/volutrauma, atelectrauma, and biotrauma may lead to ECM damage [64–68]. Low tidal volume (V_T) may lead to damage to the peripheral airways and interstitium via atelectrauma, whereas positive end-expiratory pressure (PEEP) may negate such alterations [65]. Higher V_T may also induce lung damage [66], with injury attributable to increased transpulmonary pressure, maldistribution of intrathoracic pressures, alterations of vascular flows, and reduction of lymphatic drainage of the lung. The latter may increase interstitial fluid volume, and abnormally distributed pressure may increase mechanical stress on the ECM. High V_T increases the expression of versican, HS-PG, and biglycan in lung tissue, thereby stimulating inflammation [67, 68].

Higher peak airway pressures increase type III procollagen (PCIII) mRNA expression (94). PCIII, the earliest collagen to undergo remodeling during lung fibrogenesis, is non-specific for lung injury, but has been utilized as a preliminary indicator of lung parenchyma remodeling [69].

Although the hydrostatic pressure of the interstitium (P_i) is negative in healthy lungs, P_i increases in mild edema, and approaches zero during severe edema. The negative P_i of the normal state regulates and maintains fluid filtration into the interstitium. In the mild edematous state, the P_i increases significantly with only a small increase in interstitial fluid volume, an attenuation which can be explained by low tissue compliance. This “stiffness” of the fibrous components of the ECM halts the movement of fluid into the interstitial space, impeding progression from mild to severe pulmonary edema [1, 69].

Mechanical ventilation leads to damage of GAGs and PGs in the pulmonary ECM, including HS-PG and CS-PG. Fragmentation of HS-PG and CS-PG results in pulmonary edema [70–73].

MMP-2 is effective mainly in the degradation of type IV collagen and other basement membrane components. Most MMPs are not active in normal healthy tissues, but are expressed in diseased tissues that are inflamed or undergoing repair and remodeling [33]. MMP-2 and MMP-9 are increased during mechanical ventilation, depending on the amplitude of V_T . Mechanical ventilation may enhance the degradation capabilities of MMPs, causing GAG shedding [71].

Effects of mechanical ventilation on the ECM in lungs affected by ARDS

Despite advances in ARDS management, autopsies show pulmonary fibrosis in >50% of patients [74]. Abnormal lung remodeling may be profoundly affected by different ventilator settings such as V_T , PEEP, airway and transpulmonary pressures, and respiratory rate, which can

promote interstitial ECM damage in ARDS [75]. A summary of ECM changes associated with VILI is presented in Fig. 1B.

VT and PEEP

Mechanical ventilation using high V_T has been associated with damage to GAGs, which may lead to increased lung edema [76–78] and inflammation [79], the latter through the interaction of GAGs with chemokines (e.g. IL-8) [80]. Additionally, high V_T can induce lung fibrosis through secretion of extracellular vesicles, and this might be associated with activation of the c-Jun N-terminal kinase (JNK) signaling pathway [81]. Inhibition of the JNK pathway may reduce the severity of fibrosis in vivo. Therefore, inhibition of extracellular vesicle secretion and activation of the JNK signaling pathway are promising strategies for treating pulmonary fibrosis induced by mechanical ventilation.

The actual value of V_T relative to inflation capacity and different patterns of increasing V_T may affect the ECM in experimental ARDS [82]. An abrupt increase to high V_T leads to heightened expression of MMP-9 and syndecan, which may contribute to lung inflammation. MMPs are secreted by fibroblasts via the action of extracellular matrix metalloproteinase inducer [83, 84] and the MMP inhibitor prinomastat decreases lung injury [85]. Some fragmented ECM proteins, called matrikines (elastin, osteopontin, and versican), can act as ligands to interact with certain receptors [86], leading to inflammation [87].

Even at low mechanical power [88], mechanical ventilation with high V_T also affects the ECM by increasing MMP-9 and syndecan. This observation is in contrast with the hypothesis that so long as mechanical power is kept below a safe threshold, high V_T should not be injurious. Therefore, to mitigate VILI, controlling V_T seems to determine the importance of controlling respiratory rate.

High PEEP levels may lead to increased stress in lung parenchyma, ECM, and lung vessels. At lower V_T , PEEP appears protective against VILI, preventing GAG shedding [89], whereas, higher PEEP increased the expression of procollagen, fibronectin, transforming growth factor (TGF)- β 1, and basic fibroblast growth factor [90].

Mechanical stress can damage the ECM by affecting gene expression of the connective tissue growth factor (CTGF) [91], thus increasing TGF- β and promoting the synthesis of collagens I and III [92–94]. TGF- β can potentially contribute to alveolar damage and the development of pulmonary edema because it hinders lung fluid clearance [95, 96].

Recruitment maneuvers

The influence of RMs on ECM injury response to ventilation has been explored experimentally [97–99]. In this

line, RMs (40 cmH₂O continuous positive airway pressure for 40 s) resulted in differing ECM damage when applied in lungs with ARDS [97]. In models of pulmonary and extrapulmonary ARDS with similar mechanical compromise [98], RMs increase PCIII expression only in pulmonary ARDS. The effects of abrupt, gradual, and more gradual increments in PEEP [99] were also studied in experimental ARDS. Both gradual increment groups were associated with a decrease in gene expression of syndecan and decorin, emphasizing the relative benefit of gradual PEEP increments for patients with ARDS.

Transpulmonary pressure

Transpulmonary pressure represents the stress imposed locally on the lung parenchyma and, therefore, the risk of VILI. Increasing global transpulmonary pressure from 5 to 20 cmH₂O has been associated with ~tenfold greater number of endothelial and epithelial breaks [100]. The effects of pressure and volume on lung tissue strips were evaluated using oscillation to induce stress. An increase in PCIII expression was found with stress induced by pressure (representing force) but not by volume (representing amplitude) [78]. The relationship between PCIII and force was linear (with amplitude held constant). That study suggests the existence of a *threshold* level of stress, whereby increasing the volume (amplitude) modestly may not increase stress to the threshold level, whereas increasing the amplitude further might do so. Crossing the threshold would then stimulate fibroblasts.

Different combinations of V_T and PEEP generate different transpulmonary driving pressures in experimental ARDS. In one comparative study, the combination of low V_T and PEEP (low transpulmonary driving pressure) resulted in the least PCIII expression, regardless of the presence of alveolar collapse [101].

Different modes of mechanical ventilation

In experimental ARDS, fibroblasts are activated according to the mode of mechanical ventilation. Time-controlled adaptive ventilation, compared with volume-controlled ventilation, led to less ECM damage due to better distribution of transpulmonary pressure [104]. With assisted mechanical ventilation, Neurally Adjusted Ventilatory Assist (NAVA), variable pressure support ventilation (Noisy PSV), and conventional pressure-controlled ventilation (PCV) resulted in similar lung injuries and incidence of asynchrony [102]. Noisy PSV led to lower PCIII expression than NAVA and PCV, which may be associated with different lung distribution of stress and strain. Regardless of the mode of ventilation (PCV *versus* PSV), sigh decreased PCIII expression in pulmonary ARDS but increased PCIII in extrapulmonary ARDS

[103], suggesting the importance of ARDS etiology on the susceptibility of ECM to damage [104].

In short, changes in V_T , PEEP, recruitment maneuver, transpulmonary pressure, and modes of mechanical ventilation affect the ECM differently.

ECM damage and inflammation

Mechanical ventilation with high peak inspiratory pressure elicits early signs of inflammation, including changes in the ECM [105]. GAGs and PGs regulate inflammatory responses in the lungs. Endocan is increased in ARDS patients and is thought to be a useful marker to indicate the progression of organ dysfunction [106]. GAG and PG fragments can activate toll-like receptors [107], promote leukocyte adhesion and migration, as well as activate MMP-2 [108].

Clinical implications and future perspectives

Identifying early markers of ECM damage and lung injury holds promise for implementation of preventive strategies against ARDS, particularly in patients supported by mechanical ventilation [16]. Early detection facilitates timely interventions to mitigate lung injury, thereby improving outcomes [109]. Timely intervention and risk stratification are paramount to improving respiratory management [110]. Key potential biomarkers include urinary desmosine levels, indicative of ECM degradation and lung damage; surfactant proteins (SPs) reflecting alveolar-capillary barrier integrity; inflammatory cytokines such as IL-6 and IL-8, highlighting inflammation; and plasma biomarkers such as angiotensin-2 and receptor for advanced glycation end-products (RAGE), associated with endothelial and epithelial cell damage, respectively [111]. These biomarkers could revolutionize the management of patients at risk for ARDS by enabling personalized, lung-protective strategies and dynamic care adjustments [112]. However, the clinical application of these biomarkers requires further validation to confirm their predictive value and cost-effectiveness [113].

McClintock et al. [114] found that ARDS patients who died had a higher desmosine-to-creatinine ratio than ARDS patients who survived. They found that the increase in urine desmosine levels in patients ventilated with lower V_T was attenuated, meaning less elastin degradation, and the mortality rate was lower. Tenholder et al. [115] found that excreted desmosine levels were significantly higher in ARDS patients than in patients with cardiogenic pulmonary edema and non-pulmonary edema. These findings suggest that simple laboratory tests eventually might be used to identify the presence of elastin degeneration products, such as desmosine, thereby predicting the onset of ARDS or iatrogenic lung injury in mechanically ventilated patients.

Optimization of mechanical ventilation strategies, including the use of lower V_T , PEEP, and prone positioning, appears crucial for minimizing lung injury in patients with or at risk of ARDS [116]. These interventions may be informed by understanding the dynamics of the ECM and early biomarkers of lung injury [117], guiding the adjustment of ventilation parameters to protect lung tissue. There are some pre-clinical studies that tried to use biomarkers to identify lung damage according to specific ventilatory strategies [82, 99, 118–120]. In a very elegant study, Ranieri et al. [121] reported that non-protective mechanical ventilation can induce a cytokine response that may be attenuated by a strategy to minimize overdistention and recruitment/derecruitment of the lung. There are several obstacles when evaluating biomarkers in mechanically ventilated patients with ARDS, such as: the moment of analysis (the peak of biomarkers varies according to the time course of the disease), risk factors of ARDS (e.g. diabetes, immunosuppressors), and ARDS etiology [in pulmonary versus extrapulmonary ARDS, earlier lung epithelial cell damage is observed with the predominance of specific biomarkers (e.g. SP-D, RAGE)] [122]. To mitigate obstacles presented by the heterogeneous population with ARDS, personalized mechanical ventilation strategies should be applied [122].

Pharmacological interventions targeting ECM remodeling and inflammation offer promising strategies for mitigating lung injury by preserving ECM integrity and promoting lung repair [123]. Key approaches include the use of MMP inhibitors, anti-inflammatory agents, such as corticosteroids and cytokine inhibitors (e.g. IL-6 inhibitor), and growth factors (TGF- β , vascular endothelial growth factor, and epidermal growth factor) that promote cell proliferation and repair of damaged lung tissues, which is essential for maintaining ECM integrity and restoring lung function [124].

Stern et al. [125] detected levels of keratinocyte growth factor (KGF) in bronchoalveolar lavage fluids of ARDS patients, suggesting that KGF might reflect fibroblast activation after epithelial damage. A randomized controlled trial by McAuley et al. [126] revealed that KGF, which was expected to aid ECM repair, did not improve and even worsened outcomes in ARDS patients, challenging the notion that matrix repair alone can benefit VILI patients. This result underscores the complexities of applying ECM-targeted therapies in clinical settings, highlighting the delicate balance required in ECM management, the multifaceted nature of ARDS and VILI, and the need for precise timing, dosage, and patient selection in treatments.

Such interventions aim to address the underlying causes of lung injury, combining efforts to protect the ECM, reduce inflammation, and enhance tissue repair

[127]. Although promising, their clinical application requires further research to optimize their use, considering potential side effects and the balance between therapeutic benefits and risks [127].

The development of advanced imaging techniques and diagnostic tools is poised to revolutionize the real-time assessment of ECM changes and lung tissue damage [128]. Innovations in imaging technologies are expected to enable clinicians to visualize ECM alterations and lung injury with unprecedented detail and in real time [129]. These advancements will likely incorporate machine learning algorithms to enhance image analysis, providing more accurate and timely diagnostics.

Regenerative medicine, particularly through strategies such as stem cell therapy and ECM replacement, holds promise for repairing damaged lung tissue [130]. Ongoing research is focused on developing bioengineered ECM scaffolds that closely mimic the natural lung matrix, providing a conducive environment for tissue regeneration [131]. Progress in this area could lead to breakthrough therapies for conditions previously deemed irreversible [132], transforming the treatment landscape for lung diseases.

The advent of 'Omics' technologies—encompassing genomics, proteomics, metabolomics, and more—has revolutionized our ability to study diseases at a molecular level, offering unprecedented insights into the complex biological processes underpinning health and disease [133]. In the context of investigating the ECM, and specifically the interstitial ECM, these technologies present both unique opportunities and significant challenges [134].

One of the primary opportunities afforded by 'Omics' approaches is the comprehensive profiling of the ECM composition and the dynamic changes it undergoes in response to mechanical ventilation and other stressors [135]. For instance, proteomics can elucidate the intricate array of proteins that constitute the interstitial ECM, identifying alterations in collagen, elastin, fibronectin, and other matrix proteins that are pivotal to lung structure and function [136]. Similarly, metabolomics can reveal changes in the biochemical environment within the ECM that may influence cell–matrix interactions, tissue repair, and fibrosis [136]. Such detailed molecular characterization can uncover new biomarkers of ECM damage and potential therapeutic targets to VILI [137].

However, improving the specificity of 'Omics' technologies in order to distinguish the interstitial ECM from origins in other lung structures presents a significant challenge [138]. The lung's complex architecture, comprising various cell types, blood vessels, and airspaces, intertwined with the ECM, means that 'Omics' analyses often capture a composite snapshot of this heterogeneous

environment [138]. This can confound the interpretation of data, making it difficult to attribute observed molecular changes specifically to the interstitial ECM [139].

To address this challenge, investigators can employ targeted approaches within 'Omics' studies to enhance specificity for the interstitial ECM [140]. Advanced sample preparation techniques, such as laser capture microdissection, enable the isolation of specific tissue regions enriched in interstitial ECM for analysis [140, 141]. Additionally, integrating 'Omics' data with spatially resolved techniques, such as imaging mass spectrometry or single-cell RNA sequencing, can provide contextual insights into where specific ECM components are altered within the lung tissue [140]. Such integrative approaches can help delineate the molecular signature of the interstitial ECM from confounding structures, offering a more precise understanding of its role in lung pathology.

The incorporation of computational modeling into the study of lung mechanics and pathology presents a promising avenue to dissect the complex contributions of different factors, including the interstitial ECM and surfactant, to lung function and response to injury [142]. Computational models offer a unique framework for simulating lung physiology and pathology, allowing for the isolation and manipulation of variables in ways that are not feasible in experimental or clinical settings [143].

Specifically, computational models can be designed to simulate the mechanical properties of the lung's interstitial ECM, such as elasticity, stiffness, and resistance to deformation [142]. By adjusting these parameters, researchers can evaluate how changes in the ECM, akin to those induced by mechanical ventilation or disease, influence lung function [142]. This fine tuning includes the ability to simulate the effects of ECM degradation, fibrosis, and altered matrix composition on lung compliance, gas-exchange efficiency, and susceptibility to injury [142].

Moreover, computational modeling can facilitate the exploration of how interventions aimed at preserving or restoring ECM integrity, such as the administration of ECM-protective agents or regenerative therapies, might interact with surfactant therapy in the management of lung diseases [144]. This includes predicting outcomes of combined treatments and identifying optimal therapeutic windows and dosages [144]. The challenge lies in the development of sufficiently detailed and accurate models that faithfully represent the complexities of lung structure and function [142].

To advance our understanding of VILI and the role of ECM, future research should focus on developing and applying techniques capable of distinguishing between interstitial and intraluminal ECM changes [145]. Innovative imaging techniques, molecular markers, and

computational models may offer new insights into compartment-specific ECM dynamics [146]. Such research is essential for identifying targeted interventions that can mitigate the adverse effects of mechanical ventilation on lung structure and function.

Conclusions

The ECM plays an important role in the formation of VILI. The main process is the shedding of GAGs and fragmentation of PGs caused by mechanical stress. Reduced lymphatic drainage may cause increased interstitial volume and promote ECM damage, and the abnormal distribution of pressure may lead to excessive mechanical stress on the ECM. Less GAG shedding occurs in spontaneous breathing than in mechanical ventilation, and mechanical ventilation at higher V_{T_s} causes more ECM damage than mechanical ventilation at lower V_{T_s} . GAG shedding and PG fragmentation may lead to the activation of proinflammatory processes, immune responses, and fibrosis. MMP activation due to GAG shedding seems to be the main driving factor of damage to the host because it can degrade several ECM components. Ventilation using PEEP is protective against GAG damage, although overdilatation may stimulate lung fibrogenesis.

Moreover, the inability to differentiate between interstitial and intraluminal ECM remodeling presents a notable challenge in translating research findings into clinical practice. This limitation underscores the complexity of ECM dynamics in the lung and suggests that our understanding of VILI's pathogenesis remains incomplete. Recognizing this gap is crucial for interpreting current research and for guiding future studies aimed at unraveling the distinct roles of ECM compartments in lung injury and repair.

Abbreviations

ARDS	Acute respiratory distress syndrome
CC-16	Club cell secretory protein-16
CS-PG	Chondroitin sulfate-proteoglycan
DS-PG	Dermatan sulfate-proteoglycan
ECM	Extracellular matrix
GAGs	Glycosaminoglycans
HS-PG	Heparan sulfate-proteoglycan
IL	Interleukin
JNK	C-Jun N-terminal kinase
KGF	Keratinocyte growth factor
MMPs	Matrix metalloproteinases
PCIII	Type III procollagen
PCV	Pressure-controlled ventilation
PEEP	Positive end-expiratory pressure
Pi	Hydrostatic pressure of the interstitium
RAGE	Receptor for advanced glycation end-products
RMs	Recruitment maneuvers
TGF	Transforming growth factor
TIMPs	Tissue inhibitors of metalloproteinases
VCAM-1	Vascular cell adhesion molecule 1
VILI	Ventilator-induced lung injury
V_T	Tidal volume

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Author contributions

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Availability of data and materials

The data supporting the findings of this study are available within the article.

Declarations

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Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

- Pelosi P, Rocco PR, Negrini D, Passi A. The extracellular matrix of the lung and its role in edema formation. *An Acad Bras Cienc.* 2007;79(2):285–97.
- Plataki M, Hubmayr RD. The physical basis of ventilator-induced lung injury. *Expert Rev Respir Med.* 2010;4(3):373–85.
- Avignon PD, Hedenstrom G, Hedman C. Pulmonary complications in respirator patients. *Acta Med Scand Suppl.* 1956;316:86–90.
- Humphrey JD, Dufresne ER, Schwartz MA. Mechanotransduction and extracellular matrix homeostasis. *Nat Rev Mol Cell Biol.* 2014;15(12):802–12.
- Handorf AM, Zhou Y, Halanski MA, Li WJ. Tissue stiffness dictates development, homeostasis, and disease progression. *Organogenesis.* 2015;11(1):1–15.
- Jiang Y, Zhang H, Wang J, Liu Y, Luo T, Hua H. Targeting extracellular matrix stiffness and mechanotransducers to improve cancer therapy. *J Hematol Oncol.* 2022;15(1):34.
- Davidovich N, DiPaolo BC, Lawrence GG, Chhour P, Yehya N, Margulies SS. Cyclic stretch-induced oxidative stress increases pulmonary alveolar epithelial permeability. *Am J Respir Cell Mol Biol.* 2013;49(1):156–64.
- Gattazzo F, Urciuolo A, Bonaldo P. Extracellular matrix: a dynamic microenvironment for stem cell niche. *Biochim Biophys Acta.* 2014;1840(8):2506–19.

9. Di X, Gao X, Peng L, Ai J, Jin X, Qi S, et al. Cellular mechanotransduction in health and diseases: from molecular mechanism to therapeutic targets. *Signal Transduct Target Ther.* 2023;8(1):282.
10. Tomlin H, Piccinini AM. A complex interplay between the extracellular matrix and the innate immune response to microbial pathogens. *Immunology.* 2018;155(2):186–201.
11. White ES. Lung extracellular matrix and fibroblast function. *Ann Am Thorac Soc.* 2015;12(Suppl 1):30–3.
12. Burgstaller G, Oehrle B, Gerckens M, White ES, Schiller HB, Eickelberg O. The instructive extracellular matrix of the lung: basic composition and alterations in chronic lung disease. *Eur Respir J.* 2017;50(1):1601805.
13. Burgess JK, Mauad T, Tjin G, Karlsson JC, Westergren-Thorsson G. The extracellular matrix: The under-recognized element in lung disease? *J Pathol.* 2016;240(4):397–409.
14. Bennet TJ, Randhawa A, Hua J, Cheung KC. Airway-on-a-chip: designs and applications for lung repair and disease. *Cells.* 2021;10(7):1602.
15. Krischer JM, Albert K, Pfaffenroth A, Lopez-Rodriguez E, Ruppert C, Smith BJ, et al. Mechanical ventilation-induced alterations of intracellular surfactant pool and blood-gas barrier in healthy and pre-injured lungs. *Histochem Cell Biol.* 2021;155(2):183–202.
16. Ito JT, Lourenço JD, Righetti RF, Tibério I, Prado CM, Lopes F. Extracellular matrix component remodeling in respiratory diseases: What has been found in clinical and experimental studies? *Cells.* 2019;8(4):342.
17. Winkler J, Abisoye-Ogunniyan A, Metcalf KJ, Werb Z. Concepts of extracellular matrix remodeling in tumour progression and metastasis. *Nat Commun.* 2020;11(1):5120.
18. Mecham RP. Overview of extracellular matrix. *Curr Protoc Cell Biol.* 2001;Chapter 10:Unit 10.1.
19. Naba A, Clauser KR, Hoersch S, Liu H, Carr SA, Hynes RO. The matrisome: in silico definition and in vivo characterization by proteomics of normal and tumor extracellular matrices. *Mol Cell Proteomics.* 2012;11(4):M111.014647.
20. Grinnell F, Billingham RE, Burgess L. Distribution of fibronectin during wound healing in vivo. *J Invest Dermatol.* 1981;76(3):181–9.
21. Mao Y, Schwarzbauer JE. Stimulatory effects of a three-dimensional microenvironment on cell-mediated fibronectin fibrillogenesis. *J Cell Sci.* 2005;118(Pt 19):4427–36.
22. Lensenlink EA. Role of fibronectin in normal wound healing. *Int Wound J.* 2015;12(3):313–6.
23. Sampson PM, Boyd RB, Pietra GG, Fishman AP. Glycosaminoglycan biosynthesis in the isolated perfused rat lung. *J Appl Physiol Respir Environ Exerc Physiol.* 1984;57(6):1648–54.
24. In: Varki A, Cummings RD, Esko JD, Freeze HH, Stanley P, Bertozzi CR, et al., editors. *Essentials of Glycobiology.* Cold Spring Harbor (NY): Cold Spring Harbor Laboratory Press. Copyright © 2009, The Consortium of Glycobiology Editors, La Jolla, California; 2009.
25. Schlorke D, Thomas L, Samsonov SA, Huster D, Arnhold J, Pichert A. The influence of glycosaminoglycans on IL-8-mediated functions of neutrophils. *Carbohydr Res.* 2012;356:196–203.
26. Olsson U, Ostergren-Lundén G, Moses J. Glycosaminoglycan-lipoprotein interaction. *Glycoconj J.* 2001;18(10):789–97.
27. Souza-Fernandes AB, Pelosi P, Rocco PR. Bench-to bedside review: the role of glycosaminoglycans in respiratory disease. *Crit Care.* 2006;10(6):237.
28. Bosman FT, Stamenkovic I. Functional structure and composition of the extracellular matrix. *J Pathol.* 2003;200(4):423–8.
29. Gill S, Wight TN, Frevort CW. Proteoglycans: key regulators of pulmonary inflammation and the innate immune response to lung infection. *Anat Rec.* 2010;293(6):968–81.
30. Andersson-Sjöland A, Hallgren O, Rolandsson S, Weitoft M, Tykesson E, Larsson-Callerfelt AK, et al. Versican in inflammation and tissue remodeling: the impact on lung disorders. *Glycobiology.* 2015;25(3):243–51.
31. Shi L, Herrmann J, Bou Jawde S, Bates JHT, Nia HT, Suki B. Modeling the influence of gravity and the mechanical properties of elastin and collagen fibers on alveolar and lung pressure-volume curves. *Sci Rep.* 2022;12(1):12280.
32. Elkington PT, Friedland JS. Matrix metalloproteinases in destructive pulmonary pathology. *Thorax.* 2006;61(3):259–66.
33. Lanchou J, Corbel M, Tanguy M, Germain N, Boichot E, Theret N, et al. Imbalance between matrix metalloproteinases (MMP-9 and MMP-2) and tissue inhibitors of metalloproteinases (TIMP-1 and TIMP-2) in acute respiratory distress syndrome patients. *Crit Care Med.* 2003;31(2):536–42.
34. Shetty AK, Zanirati G. The interstitial system of the brain in health and disease. *Aging Dis.* 2020;11(1):200–11.
35. Garoffolo G, Pesce M. Mechanotransduction in the cardiovascular system: from developmental origins to homeostasis and pathology. *Cells.* 2019;8(12):1607.
36. Schwartz MA. Integrins and extracellular matrix in mechanotransduction. *Cold Spring Harb Perspect Biol.* 2010;2(12):a005066.
37. Burrigide K, Chrzanowska-Wodnicka M. Focal adhesions, contractility, and signaling. *Annu Rev Cell Dev Biol.* 1996;12:463–518.
38. Xu Y, Zhao R. Force-sensing micropillar arrays for cell mechanics and mechanobiology. In: Liu X, Sun Y, editors. *Micro and nano systems for biophysical studies of cells and small organisms.* New York: Academic Press; 2021. p. 23–42.
39. Provenzano PP, Keely PJ. Mechanical signaling through the cytoskeleton regulates cell proliferation by coordinated focal adhesion and Rho GTPase signaling. *J Cell Sci.* 2011;124(Pt 8):195–205.
40. Spasic M, Maki K, Jacobs CR. 5.6 Effects of mechanical stress on cells. In: Ducheyne P, editor. *Comprehensive biomaterials II.* Oxford: Elsevier; 2017. p. 102–14.
41. Canales Coutiño B, Mayor R. Mechanosensitive ion channels in cell migration. *Cells Dev.* 2021;166:203683.
42. Chuang YC, Chen CC. Force from filaments: the role of the cytoskeleton and extracellular matrix in the gating of mechanosensitive channels. *Front Cell Dev Biol.* 2022;10:886048.
43. Hamza A, Amit J, Elizabeth LE, Medha MP, Michael DC, Wendy FL. Ion channel mediated mechanotransduction in immune cells. *Curr Opin Solid State Mater Sci.* 2021;25(6):100951.
44. Geng J, Zhao Q, Zhang T, Xiao B. In touch with the mechanosensitive piezo channels: structure, ion permeation, and mechanotransduction. *Curr Top Membr.* 2017;79:159–95.
45. Martinac B. 2021 Nobel Prize for mechanosensory transduction. *Biophys Rev.* 2022;14(1):15–20.
46. He H, Zhou J, Xu X, Zhou P, Zhong H, Liu M. Piezo channels in the intestinal tract. *Front Physiol.* 2024;15:1356317.
47. Nonomura K, Woo SH, Chang RB, Gillich A, Qiu Z, Francisco AG, et al. Piezo2 senses airway stretch and mediates lung inflation-induced apnoea. *Nature.* 2017;541(7636):176–81.
48. Samanta A, Hughes TET, Moiseenkova-Bell VY. Transient receptor potential (TRP) channels. *Subcell Biochem.* 2018;87:141–65.
49. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature.* 1997;389(6653):816–24.
50. Feliciangeli S, Chatelain FC, Bichet D, Lesage F. The family of K2P channels: salient structural and functional properties. *J Physiol.* 2015;593(12):2587–603.
51. Schwingshackl A. The role of stretch-activated ion channels in acute respiratory distress syndrome: finally a new target? *Am J Physiol Lung Cell Mol Physiol.* 2016;311(3):L639–52.
52. Zyrianova T, Lopez B, Olcese R, Belperio J, Waters CM, Wong L, et al. K(2P)2.1 (TREK-1) potassium channel activation protects against hyperoxia-induced lung injury. *Sci Rep.* 2020;10(1):22011.
53. Lele TP, Dickinson RB, Gundersen GG. Mechanical principles of nuclear shaping and positioning. *J Cell Biol.* 2018;217(10):3330–42.
54. Dahl KN, Ribeiro AJ, Lammerding J. Nuclear shape, mechanics, and mechanotransduction. *Circ Res.* 2008;102(11):1307–18.
55. Wagh K, Ishikawa M, Garcia DA, Stavreva DA, Upadhyaya A, Hager GL. Mechanical regulation of transcription: recent advances. *Trends Cell Biol.* 2021;31(6):457–72.
56. Lugano R, Ramachandran M, Dimberg A. Tumor angiogenesis: causes, consequences, challenges and opportunities. *Cell Mol Life Sci.* 2020;77(9):1745–70.
57. Lu P, Takai K, Weaver VM, Werb Z. Extracellular matrix degradation and remodeling in development and disease. *Cold Spring Harb Perspect Biol.* 2011;3(12):a005058.
58. Bonnans C, Chou J, Werb Z. Remodelling the extracellular matrix in development and disease. *Nat Rev Mol Cell Biol.* 2014;15(12):786–801.
59. Wang K, Wen D, Xu X, Zhao R, Jiang F, Yuan S, et al. Extracellular matrix stiffness: the central cue for skin fibrosis. *Front Mol Biosci.* 2023;10:1132353.

60. Janson IA, Putnam AJ. Extracellular matrix elasticity and topography: material-based cues that affect cell function via conserved mechanisms. *J Biomed Mater Res A*. 2015;103(3):1246–58.
61. Walma DAC, Yamada KM. The extracellular matrix in development. *Development*. 2020;147(10):dev175596.
62. Mierke CT. Extracellular matrix cues regulate mechanosensing and mechanotransduction of cancer cells. *Cells*. 2024;13(1):96.
63. Pang X, He X, Qiu Z, Zhang H, Xie R, Liu Z, et al. Targeting integrin pathways: mechanisms and advances in therapy. *Signal Transduct Target Ther*. 2023;8(1):1.
64. Beitler JR, Malhotra A, Thompson BT. Ventilator-induced Lung Injury. *Clin Chest Med*. 2016;37(4):633–46.
65. D'Angelo E, Pecchiari M, Della Valle P, Koutsoukou A, Milic-Emili J. Effects of mechanical ventilation at low lung volume on respiratory mechanics and nitric oxide exhalation in normal rabbits. *J Appl Physiol*. 2005;99(2):433–44.
66. Pinheiro de Oliveira R, Hetzel MP, dos Anjos Silva M, Dallegre D, Friedman G. Mechanical ventilation with high tidal volume induces inflammation in patients without lung disease. *Crit Care*. 2010;14(2):R39.
67. Pelosi P, Negrini D. Extracellular matrix and mechanical ventilation in healthy lungs: back to baro/volutrauma? *Curr Opin Crit Care*. 2008;14(1):16–21.
68. Pelosi P, Rocco PR. Effects of mechanical ventilation on the extracellular matrix. *Intens Care Med*. 2008;34(4):631–9.
69. Passi A, Negrini D, Albertini R, De Luca G, Miserocchi G. Involvement of lung interstitial proteoglycans in development of hydraulic- and elastase-induced edema. *Am J Physiol*. 1998;275(3):L631–5.
70. Perlman CE, Lederer DJ, Bhattacharya J. Micromechanics of alveolar edema. *Am J Respir Cell Mol Biol*. 2011;44(1):34–9.
71. Moriondo A, Pelosi P, Passi A, Viola M, Marozzi C, Severgnini P, et al. Proteoglycan fragmentation and respiratory mechanics in mechanically ventilated healthy rats. *J Appl Physiol*. 2007;103(3):747–56.
72. Negrini D, Passi A, de Luca G, Miserocchi G. Pulmonary interstitial pressure and proteoglycans during development of pulmonary edema. *Am J Physiol*. 1996;270(6 Pt 2):H2000–7.
73. Miserocchi G, Negrini D, Del Fabbro M, Venturoli D. Pulmonary interstitial pressure in intact in situ lung: transition to interstitial edema. *J Appl Physiol*. 1993;74(3):1171–7.
74. Papazian L, Doddoli C, Chetaille B, Gernez Y, Thirion X, Roch A, et al. A contributive result of open-lung biopsy improves survival in acute respiratory distress syndrome patients. *Crit Care Med*. 2007;35(3):755–62.
75. Marini JJ, Rocco PRM, Gattinoni L. Static and dynamic contributors to ventilator-induced lung injury in clinical practice. Pressure, energy, and power. *Am J Respir Crit Care Med*. 2020;201(7):767–74.
76. Al Jamal R, Roughley PJ, Ludwig MS. Effect of glycosaminoglycan degradation on lung tissue viscoelasticity. *Am J Physiol Lung Cell Mol Physiol*. 2001;280(2):L306–15.
77. Moriondo A, Mukenge S, Negrini D. Transmural pressure in rat initial subpleural lymphatics during spontaneous or mechanical ventilation. *Am J Physiol Heart Circ Physiol*. 2005;289(1):H263–9.
78. Garcia CS, Rocco PR, Facchinetti LD, Lassance RM, Caruso P, Deheinzelin D, et al. What increases type III procollagen mRNA levels in lung tissue: stress induced by changes in force or amplitude? *Respir Physiol Neurobiol*. 2004;144(1):59–70.
79. de Carvalho ME, Dolhnikoff M, Meireles SI, Reis LF, Martins MA, Deheinzelin D. Effects of overinflation on procollagen type III expression in experimental acute lung injury. *Crit Care*. 2007;11(1):R23.
80. Johnson Z, Proudfoot AE, Handel TM. Interaction of chemokines and glycosaminoglycans: a new twist in the regulation of chemokine function with opportunities for therapeutic intervention. *Cytokine Growth Factor Rev*. 2005;16(6):625–36.
81. Tang R, Zhou Y, Mei S, Xu Q, Feng J, Xing S, et al. Fibrotic extracellular vesicles contribute to mechanical ventilation-induced pulmonary fibrosis development by activating lung fibroblasts via JNK signalling pathway: an experimental study. *BMJ Open Respir Res*. 2023;10(1):e001753.
82. Felix NS, Samary CS, Cruz FF, Rocha NN, Fernandes MVS, Machado JA, et al. Gradually increasing tidal volume may mitigate experimental lung injury in rats. *Anesthesiology*. 2019;130(5):767–77.
83. Ellis SM, Nabeshima K, Biswas C. Monoclonal antibody preparation and purification of a tumor cell collagenase-stimulatory factor. *Cancer Res*. 1989;49(12):3385–91.
84. Biswas C, Zhang Y, DeCastro R, Guo H, Nakamura T, Kataoka H, et al. The human tumor cell-derived collagenase stimulatory factor (renamed EMMPRIN) is a member of the immunoglobulin superfamily. *Cancer Res*. 1995;55(2):434–9.
85. Foda HD, Rollo EE, Drews M, Conner C, Appelt K, Shalinsky DR, et al. Ventilator-induced lung injury upregulates and activates gelatinases and EMMPRIN: attenuation by the synthetic matrix metalloproteinase inhibitor, Prinomastat (AG3340). *Am J Respir Cell Mol Biol*. 2001;25(6):717–24.
86. Duca L, Floquet N, Alix AJ, Haye B, Debelle L. Elastin as a matrikine. *Crit Rev Oncol Hematol*. 2004;49(3):235–44.
87. Yamanaka O, Yuan Y, Coulson-Thomas VJ, Gesteira TF, Call MK, Zhang Y, et al. Lumican binds ALK5 to promote epithelium wound healing. *PLoS ONE*. 2013;8(12):e82730.
88. Moraes L, Silva PL, Thompson A, Santos CL, Santos RS, Fernandes MVS, et al. Impact of different tidal volume levels at low mechanical power on ventilator-induced lung injury in rats. *Front Physiol*. 2018;9:318.
89. Moriondo A, Marozzi C, Bianchin F, Reguzzoni M, Severgnini P, Protasoni M, et al. Impact of mechanical ventilation and fluid load on pulmonary glycosaminoglycans. *Respir Physiol Neurobiol*. 2012;181(3):308–20.
90. Berg JT, Fu Z, Breen EC, Tran HC, Mathieu-Costello O, West JB. High lung inflation increases mRNA levels of ECM components and growth factors in lung parenchyma. *J Appl Physiol*. 1997;83(1):120–8.
91. Schild C, Trueb B. Mechanical stress is required for high-level expression of connective tissue growth factor. *Exp Cell Res*. 2002;274(1):83–91.
92. Lambert CA, Soudant EP, Nusgens BV, Lapière CM. Pretranslational regulation of extracellular matrix macromolecules and collagenase expression in fibroblasts by mechanical forces. *Lab Invest*. 1992;66(4):444–51.
93. Mochitate K, Pawelek P, Grinnell F. Stress relaxation of contracted collagen gels: disruption of actin filament bundles, release of cell surface fibronectin, and down-regulation of DNA and protein synthesis. *Exp Cell Res*. 1991;193(1):198–207.
94. Eckes B, Mauch C, Hüppe G, Krieg T. Downregulation of collagen synthesis in fibroblasts within three-dimensional collagen lattices involves transcriptional and posttranscriptional mechanisms. *FEBS Lett*. 1993;318(2):129–33.
95. Pittet JF, Griffiths MJ, Geiser T, Kaminski N, Dalton SL, Huang X, et al. TGF-beta is a critical mediator of acute lung injury. *J Clin Invest*. 2001;107(12):1537–44.
96. Frank J, Roux J, Kawakatsu H, Su G, Dagenais A, Berthiaume Y, et al. Transforming growth factor-beta1 decreases expression of the epithelial sodium channel alphaENaC and alveolar epithelial vectorial sodium and fluid transport via an ERK1/2-dependent mechanism. *J Biol Chem*. 2003;278(45):43939–50.
97. Farias LL, Faffe DS, Xisto DG, Santana MC, Lassance R, Prota LF, et al. Positive end-expiratory pressure prevents lung mechanical stress caused by recruitment/derecruitment. *J Appl Physiol*. 2005;98(1):53–61.
98. Riva DR, Oliveira MB, Rzezinski AF, Rangel G, Capellozi VL, Zin WA, et al. Recruitment maneuver in pulmonary and extrapulmonary experimental acute lung injury. *Crit Care Med*. 2008;36(6):1900–8.
99. Fernandes MVS, Rocha NN, Felix NS, Rodrigues GC, Silva LHA, Coelho MS, et al. A more gradual positive end-expiratory pressure increase reduces lung damage and improves cardiac function in experimental acute respiratory distress syndrome. *J Appl Physiol*. 2022;132(2):375–87.
100. Fu Z, Costello ML, Tsukimoto K, Prediletto R, Elliott AR, Mathieu-Costello O, et al. High lung volume increases stress failure in pulmonary capillaries. *J Appl Physiol*. 1992;73(1):123–33.
101. Samary CS, Santos RS, Santos CL, Felix NS, Bentes M, Barboza T, et al. Biological impact of transpulmonary driving pressure in experimental acute respiratory distress syndrome. *Anesthesiology*. 2015;123(2):423–33.
102. Scharffenberg M, Weiss T, Wittenstein J, Krenn K, Fleming M, Biro P, et al. Practice of oxygen use in anesthesiology: a survey of the European Society of Anaesthesiology and Intensive Care. *BMC Anesthesiol*. 2022;22(1):350.
103. Moraes L, Santos CL, Santos RS, Cruz FF, Saddy F, Morales MM, et al. Effects of sigh during pressure control and pressure support ventilation in pulmonary and extrapulmonary mild acute lung injury. *Crit Care*. 2014;18(4):474.
104. Santos CL, Santos RS, Moraes L, Samary CS, Felix NS, Silva JD, et al. Effects of pressure support and pressure-controlled ventilation on lung

- damage in a model of mild extrapulmonary acute lung injury with intra-abdominal hypertension. *PLoS ONE*. 2017;12(5):e0178207.
105. Imanaka H, Shimaoka M, Matsuura N, Nishimura M, Ohta N, Kiyono H. Ventilator-induced lung injury is associated with neutrophil infiltration, macrophage activation, and TGF- β 1 mRNA upregulation in rat lungs. *Anesth Analg*. 2001;92(2):428–36.
 106. Gaudet A, Chenevier-Gobeaux C, Parmentier E, Delobel JE, Dubucquoi S, Mathieu D, et al. Endocan is a stable circulating molecule in ICU patients. *Clin Biochem*. 2017;50(15):870–7.
 107. Johnson GB, Brunn GJ, Platt JL. Cutting edge: an endogenous pathway to systemic inflammatory response syndrome (SIRS)-like reactions through Toll-like receptor 4. *J Immunol*. 2004;172(1):20–4.
 108. Iida J, Wilhelmson KL, Ng J, Lee P, Morrison C, Tam E, et al. Cell surface chondroitin sulfate glycosaminoglycan in melanoma: role in the activation of pro-MMP-2 (pro-gelatinase A). *Biochem J*. 2007;403(3):553–63.
 109. Gong MN, Schenk L, Gajic O, Mirhaji P, Sloan J, Dong Y, et al. Early intervention of patients at risk for acute respiratory failure and prolonged mechanical ventilation with a checklist aimed at the prevention of organ failure: protocol for a pragmatic stepped-wedged cluster trial of PROOFCheck. *BMJ Open*. 2016;6(6):e011347.
 110. Brown R, McKelvey MC, Ryan S, Creane S, Linden D, Kidney JC, et al. The impact of aging in acute respiratory distress syndrome: a clinical and mechanistic overview. *Front Med*. 2020;7:589553.
 111. Blondonnet R, Constantin JM, Sapin V, Jabaudon M. A Pathophysiologic approach to biomarkers in acute respiratory distress syndrome. *Dis Markers*. 2016;2016:3501373.
 112. Spadaro S, Park M, Turrini C, Tunstall T, Thwaites R, Mauri T, et al. Biomarkers for acute respiratory distress syndrome and prospects for personalised medicine. *J Inflamm*. 2019;16:1.
 113. Ou FS, Michiels S, Shyr Y, Adjei AA, Oberg AL. Biomarker discovery and validation: statistical considerations. *J Thorac Oncol*. 2021;16(4):537–45.
 114. McClintock DE, Ware LB, Eisner MD, Wickersham N, Thompson BT, Matthay MA. Higher urine nitric oxide is associated with improved outcomes in patients with acute lung injury. *Am J Respir Crit Care Med*. 2007;175(3):256–62.
 115. Tenholder MF, Rajagopal KR, Phillips YY, Dillard TA, Bennett LL, Mundie TG, et al. Urinary desmosine excretion as a marker of lung injury in the adult respiratory distress syndrome. *Chest*. 1991;100(5):1385–90.
 116. Sud S, Friedrich JO, Adhikari NK, Taccone P, Mancebo J, Polli F, et al. Effect of prone positioning during mechanical ventilation on mortality among patients with acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ*. 2014;186(10):E381–90.
 117. Abbott M, Li Y, Brochard L, Zhang H. Precision medicine using simultaneous monitoring and assessment with imaging and biomarkers to manage mechanical ventilation in ARDS. *Intensive Care Res*. 2023;3(3):195–203.
 118. Silva PL, Cruz FF, dos Samary CS, Moraes L, de Magalhães RF, de Fernandes MVS, et al. Biological response to time-controlled adaptive ventilation depends on acute respiratory distress syndrome etiology. *Crit Care Med*. 2018;46(6):609–17.
 119. de Magalhães RF, Cruz DG, Antunes MA, Fernandes MVdS, Oliveira MV, Braga CL, et al. Time-controlled adaptive ventilation versus volume-controlled ventilation in experimental pneumonia. *Crit Care Med*. 2021;49(1):140–50.
 120. Xavier PH, Fonseca ACF, Gonçalves LA, de Sousa GC, da Silva MC, de Sacramento RFM, et al. Lung injury is induced by abrupt increase in respiratory rate but prevented by recruitment maneuver in mild acute respiratory distress syndrome in rats. *Anesthesiology*. 2023;138(4):420–35.
 121. Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *JAMA*. 1999;282(1):54–61.
 122. Jabaudon M, Blondonnet R, Ware LB. Biomarkers in acute respiratory distress syndrome. *Curr Opin Crit Care*. 2021;27(1):46–54.
 123. Guo T, He C, Venado A, Zhou Y. Extracellular matrix stiffness in lung health and disease. *Compr Physiol*. 2022;12(3):3523–58.
 124. Ozkan E, Bakar-Ates F. The trinity of matrix metalloproteinases, inflammation, and cancer: a literature review of recent updates. *Antiinflamm Antiallergy Agents Med Chem*. 2020;19(3):206–21.
 125. Stern JB, Fierobe L, Paugam C, Rolland C, Dehoux M, Petiet A, et al. Keratinocyte growth factor and hepatocyte growth factor in bronchoalveolar lavage fluid in acute respiratory distress syndrome patients. *Crit Care Med*. 2000;28(7):2326–33.
 126. McAuley DF, Cross LM, Hamid U, Gardner E, Elborn JS, Cullen KM, et al. Keratinocyte growth factor for the treatment of the acute respiratory distress syndrome (KARE): a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Respir Med*. 2017;5(6):484–91.
 127. González-López A, Albaiceta GM. Repair after acute lung injury: molecular mechanisms and therapeutic opportunities. *Crit Care*. 2012;16(2):209.
 128. Wijsman PC, van Smoorenburg LH, de Bruin DM, Annema JT, Kerstjens HAM, Mets OM, et al. Imaging the pulmonary extracellular matrix. *Curr Opin Physiol*. 2021;22:100444.
 129. Ito JT, Lourenço JD, Righetti RF, Tibério IFLC, Prado CM, Lopes FDTQS. Extracellular matrix component remodeling in respiratory diseases: What has been found in clinical and experimental studies? *Cells*. 2019;8(4):342.
 130. Adamič N, Vengust M. Regenerative medicine in lung diseases: a systematic review. *Front Vet Sci*. 2023;10:1115708.
 131. Uriarte JJ, Uhl FE, Rolandsson Enes SE, Pouliot RA, Weiss DJ. Lung bioengineering: advances and challenges in lung decellularization and recellularization. *Curr Opin Organ Transplant*. 2018;23(6):673–8.
 132. de Jong D, Das JP, Ma H, Pailey Valiplackal J, Prendergast C, Roa T, et al. Novel targets, novel treatments: the changing landscape of non-small cell lung cancer. *Cancers*. 2023;15(10):2855.
 133. Dai X, Shen L. Advances and trends in omics technology development. *Front Med*. 2022;9:911861.
 134. Bons J, Pan D, Shah S, Bai R, Chen-Tanyolac C, Wang X, et al. Data-independent acquisition and quantification of extracellular matrix from human lung in chronic inflammation-associated carcinomas. *Proteomics*. 2023;23(7–8):e2200021.
 135. Hu M, Ling Z, Ren X. Extracellular matrix dynamics: tracking in biological systems and their implications. *J Biol Eng*. 2022;16(1):13.
 136. Popova NV, Jücker M. The functional role of extracellular matrix proteins in cancer. *Cancers*. 2022;14(1):238.
 137. Petersen EV, Chudakova DA, Skorova EY, Anikin V, Reshetov IV, Mynbaev OA. The extracellular matrix-derived biomarkers for diagnosis, prognosis, and personalized therapy of malignant tumors. *Front Oncol*. 2020;10:575569.
 138. Zhou Y, Horowitz JC, Naba A, Ambalavanan N, Atabai K, Balestrini J, et al. Extracellular matrix in lung development, homeostasis and disease. *Matrix Biol*. 2018;73:77–104.
 139. Hackett TL, Osei ET. Modeling extracellular matrix-cell interactions in lung repair and chronic disease. *Cells*. 2021;10(8):2145.
 140. Bingham GC, Lee F, Naba A, Barker TH. Spatial-omics: Novel approaches to probe cell heterogeneity and extracellular matrix biology. *Matrix Biol*. 2020;91–92:152–66.
 141. Domazet B, MacLennan GT, Lopez-Beltran A, Montironi R, Cheng L. Laser capture microdissection in the genomic and proteomic era: targeting the genetic basis of cancer. *Int J Clin Exp Pathol*. 2008;1(6):475–88.
 142. Neelakantan S, Xin Y, Gaver DP, Cereda M, Rizi R, Smith BJ, et al. Computational lung modelling in respiratory medicine. *J R Soc Interface*. 2022;19(191):20220062.
 143. Warnaar RSP, Mulder MP, Friesiello L, Cornet AD, Heunks LMA, Donker DW, et al. Computational physiological models for individualised mechanical ventilation: a systematic literature review focussing on quality, availability, and clinical readiness. *Crit Care*. 2023;27(1):268.
 144. Jones CL, Penney BT, Theodosiou SK. Engineering Cell-ECM-material interactions for musculoskeletal regeneration. *Bioengineering*. 2023;10(4):453.
 145. Zhao Y, Zheng X, Zheng Y, Chen Y, Fei W, Wang F, et al. Extracellular matrix: emerging roles and potential therapeutic targets for breast cancer. *Front Oncol*. 2021;11: 650453.
 146. Chaher N, Hajhosseiny R, Phinikaridou A, Botnar RM. Imaging the extracellular matrix in prevalent cardiovascular diseases. *Appl Sci*. 2020;10(11):4001.

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