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Pathophysiology of Acute Respiratory Distress Syndrome and COVID-19 Lung Injury

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KEYWORDS

• acute respiratory distress syndrome • COVID-19 • pathophysiology

KEY POINTS

- Acute respiratory distress syndrome (ARDS) is a form of noncardiogenic, permeability pulmonary edema associated with systemic inflammatory conditions and marked by diffuse alveolar damage.
- A wide spectrum of ventilation/perfusion defects, including dead space and shunt, is responsible for gas exchange impairments in ARDS.
- Focal parenchymal involvement and derecruitment in ARDS, especially common in posterior and dependent regions, affect ventilation and perfusion heterogeneity and likely contribute to ongoing lung injury due to stress propagation.
- Normal mechanisms for alveolar fluid clearance are impaired in ARDS due to alveolar epithelial injury and inactivation of surfactant.
- Trauma from ventilatory support in ARDS can be roughly divided into 2 categories involving high (barotrauma/volutrauma) and low (atelectrauma) lung volumes; the resulting adverse biologic effects of these traumatic forces on the lung parenchyma and the systemic inflammatory response are broadly termed biotrauma.
- Spontaneous breathing efforts, especially in the presence of ventilator dyssynchrony, may further aggravate lung injury due to the above mechanisms and are broadly termed patient self-inflicted lung injury (P-SILI).
- Some cases of COVID-19-related lung injury may initially present with mild reductions in compliance and less dyspnea in comparison with the degree of worrisome hypoxemia (so-called silent hypoxemia).

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- However, the overall pathophysiology and clinical course of COVID-19-related lung injury suggests that it is broadly similar to other forms of virally-mediated ARDS.

PATHOPHYSIOLOGY OF ACUTE RESPIRATORY DISTRESS SYNDROME

Acute respiratory distress syndrome (ARDS) is a complex syndrome of acute lung injury leading to noncardiogenic pulmonary edema from many causes that is heterogenous in its clinical presentation and associated with a 40% mortality rate.[1] Extensive work since its initial description in 1967 has elucidated biological pathways causing the many physiologic changes of alveolar collapse/derecruitment, reduced lung compliance, greater pulmonary vascular resistance, and gas exchange impairment that can be compounded by patient's own ventilatory response or assisted ventilatory support, due to regional heterogeneity of the underlying lung injury.

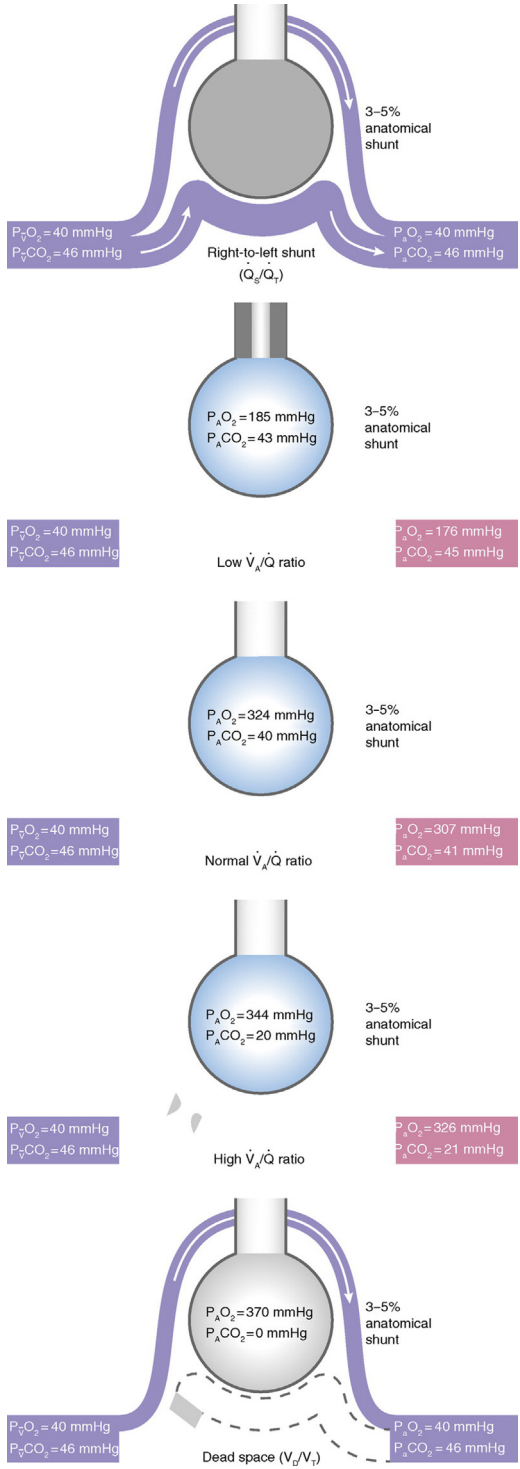
Pathogenesis of Acute Respiratory Distress Syndrome

It is useful to briefly review the pathogenesis of lung injury and repair in ARDS to understand its effects on physiology. Injury begins with activation of alveolar macrophages by microbial or cell injury products,[2] which are locally derived in primary lung injury (pulmonary ARDS) or systemically derived (extrapulmonary ARDS). Cytokine/chemokine release by macrophages recruits and activates circulating neutrophils, which release myriad inflammatory molecules. Although assisting with pathogen killing, they also injure the normally tight alveolar endothelial–epithelial barrier consisting of adherent cell-cell contacts and glycocalyx linings.[3] Alveolar type II pneumocytes secrete surfactant and along with type I pneumocytes reabsorb alveolar fluid by active ion transport back into the interstitium for lymphatic clearance.[4] As a result of loss of the normal low permeability characteristics, the alveolar space fills with an inflammatory cell-rich proteinaceous edema fluid (exudative phase of ARDS), a prime determinant of lung injury severity, alveolar collapse, and derecruitment.[5]

In the proliferative phase of ARDS, with the clearance of pathogens and damaged host cells from the alveolar space, the immune response is recalibrated to prioritize repair and restoration of normal function. This involves neutrophil apoptosis and removal, expansion of resident fibroblasts and interstitial matrix reformation, and regrowth of alveolar epithelium by differentiation of type II alveolar cells into type I cells. If the proliferative phase is impaired or prolonged, ongoing inflammation and fibroblast proliferation impair alveolar clearance and functional recovery.[6] It is likely that uncleared, insoluble proteins in the alveolar space (forming hyaline membranes observed histologically) seed the formation of fibrotic tissue by mesenchymal cells, ultimately leading to the long-term consequence of fibrosing alveolitis (fibrotic phase of ARDS) in some but not all patients.

Gas Exchange Impairment in Acute Respiratory Distress Syndrome

The consequences of the above changes to alveolar structure and histology are gas exchange impairment, increased work breathing, and dyspnea leading to respiratory failure. Alveolar flooding along with pulmonary vascular injury generates the entire spectrum of V_A/Q abnormalities from areas with reduced ventilation-to-perfusion (V_A/Q) ratios and intrapulmonary shunting to high V_A/Q ratios and dead space (**Fig. 1**). Low V_A/Q and shunt are responsible for increased venous admixture and arterial hypoxemia. Given little or no ventilation to these areas, arterial hypoxemia is


3–5% anatomical shunt
$P_{\bar{v}}O_2$ = 40 mmHg
$P_{\bar{v}}CO_2$ = 46 mmHg
Right-to-left shunt ($\dot{Q}_S/\dot{Q}_T$)
P_aO_2 = 40 mmHg
P_aCO_2 = 46 mmHg
P_AO_2 = 185 mmHg
P_ACO_2 = 43 mmHg
3–5% anatomical shunt
$P_{\bar{v}}O_2$ = 40 mmHg
$P_{\bar{v}}CO_2$ = 46 mmHg
Low $\dot{V}_A/\dot{Q}$ ratio
P_aO_2 = 176 mmHg
P_aCO_2 = 45 mmHg
P_AO_2 = 324 mmHg
P_ACO_2 = 40 mmHg
3–5% anatomical shunt
$P_{\bar{v}}O_2$ = 40 mmHg
$P_{\bar{v}}CO_2$ = 46 mmHg
Normal $\dot{V}_A/\dot{Q}$ ratio
P_aO_2 = 307 mmHg
P_aCO_2 = 41 mmHg
P_AO_2 = 344 mmHg
P_ACO_2 = 20 mmHg
3–5% anatomical shunt
$P_{\bar{v}}O_2$ = 40 mmHg
$P_{\bar{v}}CO_2$ = 46 mmHg
High $\dot{V}_A/\dot{Q}$ ratio
P_aO_2 = 326 mmHg
P_aCO_2 = 21 mmHg
P_AO_2 = 370 mmHg
P_ACO_2 = 0 mmHg
3–5% anatomical shunt
$P_{\bar{v}}O_2$ = 40 mmHg
$P_{\bar{v}}CO_2$ = 46 mmHg
Dead space (V_D/V_T)
P_aO_2 = 40 mmHg
P_aCO_2 = 46 mmHg

insensitive to global increases in ventilation. Increased F_{IO2} can improve oxygenation in low V_A/Q regions, though not in shunts. Although alveolar and interstitial edema widens the alveolar–capillary barrier, the impact of diffusion limitation in causing hypoxemia is dwarfed by contributions of low V_A/Q and shunt[7] as demonstrated by the multiple inert gas elimination technique (MIGET). Increases in alveolar oxygen with higher F_{IO2} minimize the impact of any diffusion limitation by increasing the alveolar–capillary oxygen driving gradient. Finally, intracardiac shunting can develop in patients with a preexisting patent foramen ovale, who develop elevated right heart pressures because of increased pulmonary vascular resistance (PVR).

Hypercapnia can also occur but is not incorporated into any ARDS definitions. Several aspects of CO_2 elimination in ARDS merit discussion. As is the case for oxygen uptake, V_A/Q mismatching also impairs CO_2 elimination. Although a diffusion impairment for CO_2 does not occur due to its very high solubility in blood and tissue water and a 20-fold greater diffusivity over oxygen, any failure of alveolar–capillary CO_2 equilibration (widened a-A P_{CO_2} gradient) results from rapid capillary transit times and several relatively slower steps in blood CO_2 chemistry including red cell membrane chloride–bicarbonate exchange and the Bohr-Haldane effects.[8] Both high and low V_A/Q regions (including shunt) contribute significantly to hypercapnia, as clarified using MIGET[9] because mixed venous blood flowing through low V_A/Q units enters into the systemic arterial circulation with little or no CO_2 elimination.[10] The use of the Bohr–Enghoff equation to estimate dead space with values as high as 75%[11] overestimates the magnitude of physiologic dead space in ARDS occurring from vascular obstruction and vasoconstriction.[9] Nonetheless, a rising CO_2 dead space may be associated with increased vascular resistance and right heart dysfunction indicative of vascular obstruction.[12] Increases in minute ventilation can effectively improve CO_2 elimination from less injured regions due to the steepness of the blood CO_2 dissociation curve and even cause arterial hypocapnia but become less effective as V_A/Q mismatching worsens and the increased work of breathing generates more CO_2. Ventilation of high V_A/Q regions, especially dead space ($V_A/Q > 100$), wastes respiratory effort without contributing to CO_2 elimination.[13]

Hypercapnia with protective lung ventilation is better accepted since the landmark ARDSNet study showing mortality reduction with this strategy.[14] However, whether this permissive hypercapnia itself might have benefits remains uncertain. It may have both positive and deleterious effects on the ongoing process of lung injury, such as the attenuation of lung inflammation, but results in reduced alveolar fluid clearance.[15,16]

Fig. 1. Spectrum of V_A/Q abnormalities in ARDS. The spectrum of V_A/Q abnormalities in ARDS (from top to bottom) ranging from shunt ($V_A/Q = 0$), low ventilation-to-perfusion ratio ($V_A/Q = 0.2–0.01$), normal ratio ($V_A/Q = 0.2–5$), high ventilation-to-perfusion ratio ($V_A/Q = 5–100$) to dead space ($V_A/Q =$ infinity). Typical mixed venous, alveolar (*A*), and arterial (*A*), and mixed venous (mv) P_{O_2} and P_{CO_2} values are shown. Values are those at a fractional inspired O_2 concentration of 0.5 at a hemoglobin of 15 g/dL and a respiratory exchange ratio of 0.8. (*From* Radermacher P, Maggiore SM, Mercat A. Fifty years of research in ARDS. Gas exchange in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2017; 196(8): 964-84.; with permission.)

Regional Differences in Lung Density, Ventilation, and Blood Flow in Acute Respiratory Distress Syndrome

ARDS does not affect the lung uniformly, as shown by CT imaging (**Fig. 2**). The greatest degree of edema, parenchymal densities, consolidation, and shunting are often in the dorsal and basilar regions of the lung, particularly in the supine position, the position in which most patients are maintained while on mechanical ventilation or during hemodynamic instability. However, this heterogeneity can be altered with position changes, such as with turning to the prone position.[17] Quantification of heterogeneity in lung units using MIGET demonstrates a wide range of VA/Q lung units indirectly, with a bimodal distribution of considerable shunt and elevated alveolar dead space,[18] but it provides no regional information. Advanced imaging techniques, including radiolabeled inert gas inhalation/infusion, can provide spatial resolution for the physiologic heterogeneity seen with MIGET in ARDS.[19] Areas of lowest ventilation and lowest V_A/Q (areas of CT densities) are found in gravitationally dependent regions; regional ventilation heterogeneity is greater in the supine than in the prone position (**Fig. 3**), likely a consequence of the more compressive effect of lung and soft tissue weight (cardiac and abdominal) on basilar lung regions and higher regional pleural pressure differences in the supine position.[20] Oxygenation in ARDS improves in most patients with prone positioning resulting from the reduction in regional V_A/Q heterogeneity.

Pulmonary blood flow, on the other hand, is less affected by gravitational forces and positioning,[21] as regional blood vessel density and local vascular tone are the primary

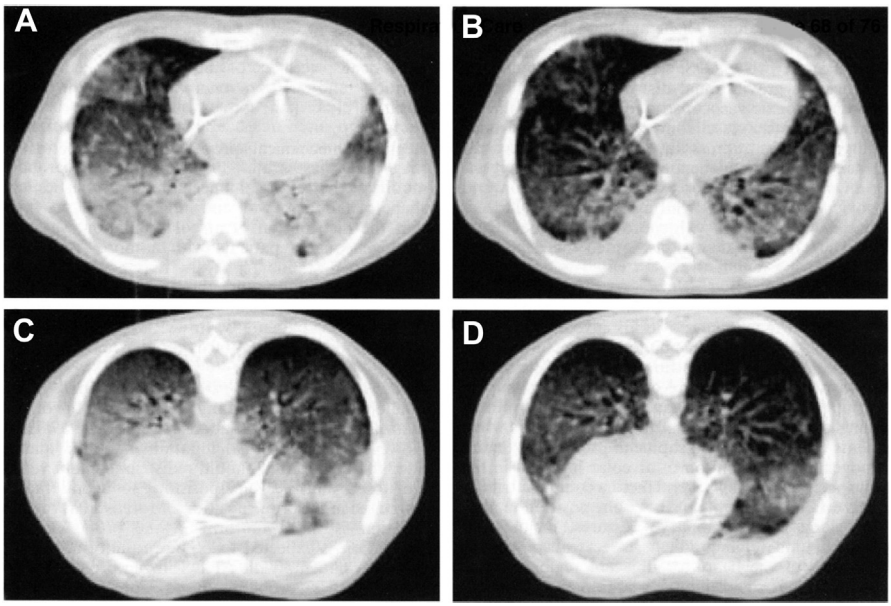


Fig. 2. Differences in lung density by CT imaging in prone vs. supine positioning. Differences in lung density by CT scanning in ARDS, taken in the supine position at end exhalation (*A*), end inspiration (*B*), and in the prone position at end exhalation (*C*) and at end inspiration (*D*). The improvement in aeration in the prone images is consistent with the more uniform V_A/Q matching and improved oxygenation with prone positioning. (*From* Kallet RH. A Comprehensive Review of Prone Position in ARDS. Respir Care. 2015; 60(11): 1660-87; with permission.)

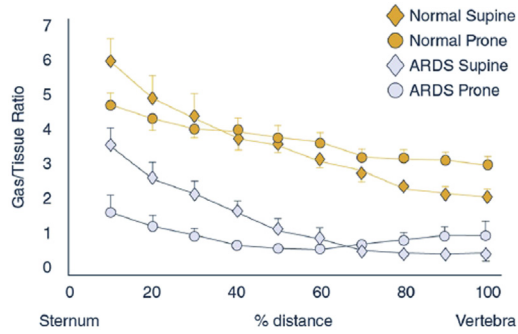


Fig. 3. Changes in lung tissue heterogeneity over the anterior-posterior plane. The gas/tissue ratios reflect the degree of uniformity of ventilated lung as a function of the distance between the sternum and the vertebrae. In the supine position, the gas/tissue ratio sharply decreases from the sternum to the vertebrae suggesting that both in normal and in patients with ARDS distending forces are about 3 times higher closer to the sternum than to the vertebrae. In prone position, the gas/tissue ratio is far more homogeneous, indicating a more even distribution of forces and more uniform ventilation throughout the lung. (*From* Guérin C, Albert RK, Beitler J, et al. Prone position in ARDS patients: why, when, how and for whom. Intensive Care Med. 2020;46(12):2385-2396. doi:10.1007/s00134-020-06306-w; with permission.)

determinants of regional perfusion. Perfusion is higher in posterior and caudal lung regions, and therefore, prone positioning (which improves ventilation in these areas) is associated with significant gas exchange improvement in most patients with ARDS. Pulmonary vascular tone is presumed to be mediated most directly by hypoxic pulmonary vasoconstriction (HPV) and hypercapnic pulmonary vasoconstriction that redirect perfusion to greater ventilated and oxygenated lung units to optimize V_A/Q matching. The only direct evidence that HPV is operative and contributes significantly to regional vascular tone in ARDS because it has never been tested formally by hypoxic gas inspiration,[22] comes from patients receiving extracorporeal membrane oxygenation in whom mean PA pressure decreased, and PVR fell 25% when the mixed venous P_{O_2} was raised from 47 to 84 mm Hg by increasing extracorporeal blood flow.[23] HPV augmentation with pulmonary vasoconstrictors (almitrine) and inhalation of pulmonary vasodilators (such as nitric oxide) to vasodilate ventilated areas are both associated with reductions in hypoxemia; the latter treatment, however, only exerts effects on ventilated lung units to which it can be delivered.[24]

Respiratory Mechanics in Acute Respiratory Distress Syndrome

Lung parenchyma is formed from millions of interdependent alveoli, which share the alveolar volume throughout the lung, preventing overdistension during inspiration and collapse during expiration.[25] This allows for parenchymal stress during inspiration to be somewhat homogenized, despite variability in alveolar size and location. In ARDS, increased permeability and loss of surfactant cause some alveoli to become flooded and unrecruitable or poorly recruitable. As a result, lung volume remaining for gas exchange shrinks, and lung compliance is reduced, though it varies widely based on disease severity from 5 to 40 mL/cmH_20,[26,27] and functional residual capacity is decreased by 20% to 30% compared with normal.[28] The volume of derecruited lung appears to roughly correlate with the degree of pulmonary shunt and gas exchange abnormalities.[29]

It has been long recognized that alveolar edema and derecruitment occur in a heterogeneous regional fashion, with dependent regions most affected.[30,31] Focal and nonfocal patterns of lung involvement in ARDS respond differently to recruitment maneuvers such as positive end-expiratory pressure (PEEP) or position change.[32] These radiographic findings reinforce the idea that the lung in ARDS can be conceptually divided into nonaerated diseased regions and aerated healthy regions. The diminished size of normal aerated lung tissue in relation to overall lung mass has been termed the "baby lung in an adult body."[26] As is clear from the radiographic studies above, the "baby lung" need not be a distinct anatomic but rather a physiologic entity, and its area can shift dramatically depending on body position.[30]

Global measurements of compliance and airway, plateau, and transpulmonary pressures may not adequately account for such regional variation in physiology. For example, there may be significant variations in pleural pressure in ARDS, especially between dependent and nondependent regions, that are not captured by a point estimate of pleural pressure via esophageal balloon and can be as high as 10 cmH_20 in cadaveric studies.[33] Additionally, airway pressure measurements may not accurately estimate local stresses in regions with airway closure, particularly in obese patients.[32]

These regional variations in compliance can lead to heterogeneous injury risk. In a process called stress concentration, local alveolar derecruitment causes inhomogeneity in distending pressures, with surrounding alveoli bearing the greatest stress. In effect, this creates a penumbra of at-risk lung units (**Fig. 4**) surrounding an area of injury that may propagate.[34,35] These areas have been termed "stress raisers" and may involve up to a quarter of the parenchyma as visualized by dynamic CT imaging. Mechano-transduction associated with shear stresses caused by cyclic atelectasis in these regions may contribute to cleavage of cell-cell adhesion molecules, further disrupting membranes and preventing alveolar clearance of edema.[36] Despite retaining grossly normal mechanical properties,[37] PET imaging demonstrates that well-aerated lung regions have abnormal permeability and higher metabolic rate, suggesting ongoing and worsening inflammation even with lung-protective ventilation.[38,39]

Though ARDS is predominantly a restrictive disorder, airway obstruction can also occur from edematous distal airways and increased lung weight causing small airway narrowing/closure, with total airway resistance elevated roughly 2-fold.[40] Expiratory flow limitation does appear to exist in ARDS and improves with PEEP though not with bronchodilators.[41] Although rapid flows and rapid changes in pressure likely exert some degree of additional stress to the lung parenchyma given its viscoelastic nature, the clinical importance of this stress is not fully known.

Alveolar and Lymphatic Fluid Clearance in Acute Respiratory Distress Syndrome

The ability of the lung to maintain a highly compliant and dry alveolar air space for efficient gas exchange at a low work of breathing cost depends upon a number of factors, including surfactant production and active vectorial alveolar epithelial sodium and water transport from the alveolar space into the interstitium for reuptake into the blood or lymphatic transport. In ARDS, the surfactant is inactivated, and alveolar epithelial injury leads to loss of fluid reabsorption (**Fig. 5**). Type I and II alveolar epithelial cells actively reabsorb sodium and fluid from the airspace via apical membrane sodium entry through epithelial sodium channels (ENaCs) driven by the concentration gradient established by sodium pumping into the interstitium by basolateral membrane energy-consuming Na^+/K^+ ATPase.[42] Chloride follows paracellularly and via cystic fibrosis transmembrane conductance regulator (CFTR)-mediated transcellular uptake[43] and water by paracellular movement and by aquaporin-5 mediated transcellular movement.[44] Fluid reabsorption rates in the isolated human lung average about 12%

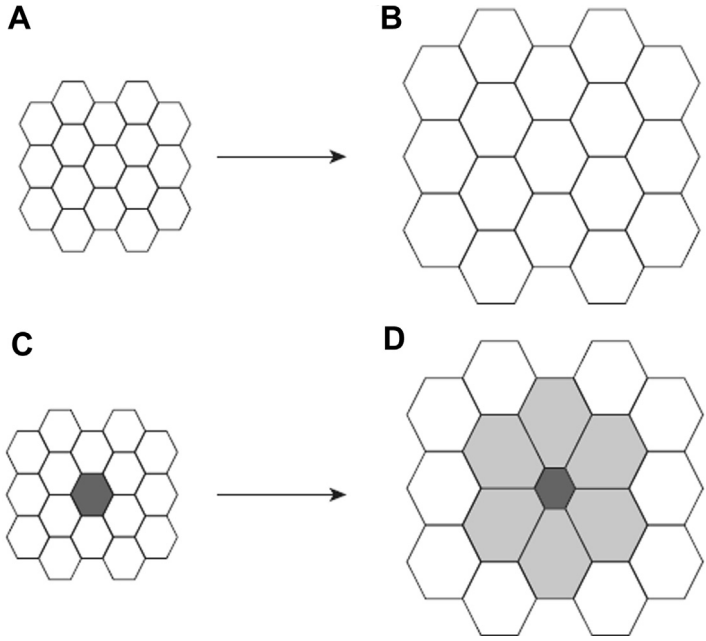


Fig. 4. Local ventilatory inhomogeneity as a stress raiser. A stress raiser is a region of early injury that leads to inhomogeneous tissue forces that apply stress and strain to surrounding neighbor regions. An equal volume of gas is introduced into an area of normal lung (*A*) and into one with a stress raiser (either a collapsed or non-air-filled region-the dark region in (*C*). In a normal lung, the introduced air with inflation is evenly distributed and leads to uniform inflation at minimal stress (*B*). In contrast, the lung with a stress raiser, when further inflated (*D*), subjects the immediate neighboring regions (colored gray) to greater stress (and potential injury) as they are inflated, but the collapsed or fluid-filled region itself is not inflated. (*From* Henderson WR, Chen L, Amato MB, Brochard LJ. Fifty years of research in ARDS. Respiratory mechanics in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2017; 196(7): 822-33; with permission.)

per hour[45] but likely are higher in vivo. Reabsorption can be stimulated several-fold by beta-2 adrenergic agonist- and corticosteroid-mediated upregulation of ENaCs and Na^+/K^+ ATPase membrane expression and activity.[42,45] Fluid clearance from the lung interstitium by lung lymphatics is mediated passively by ventilatory efforts and by active, spontaneous contractions that can be stimulated by beta-2 adrenergic drugs[46] that may enhance lymph drainage from the lung.

In conditions wherein the alveolar epithelium is not injured, such as cardiogenic pulmonary edema, beta-2 adrenergic agonists increase fluid reabsorption, but the hope that this might be realized in ARDS could not be demonstrated in 2 large clinical trials involving systemic[47] and inhaled[48] drug administration. The success in heart failure and lack of efficacy in ARDS is likely explained by a functioning intact alveolar epithelium in cardiogenic pulmonary edema and injury and denudation of the epithelium in acute lung injury, either unable to reabsorb sodium at all or keep pace with ongoing rates of microvascular leakage. The increase in alveolar surface tension with cessation of production and inactivation of surfactant in ARDS leads to a lower interstitial pressure that increases the microvascular transmural pressure gradient. This favors greater extravascular fluid accumulation for the same microvascular pressure.[49]

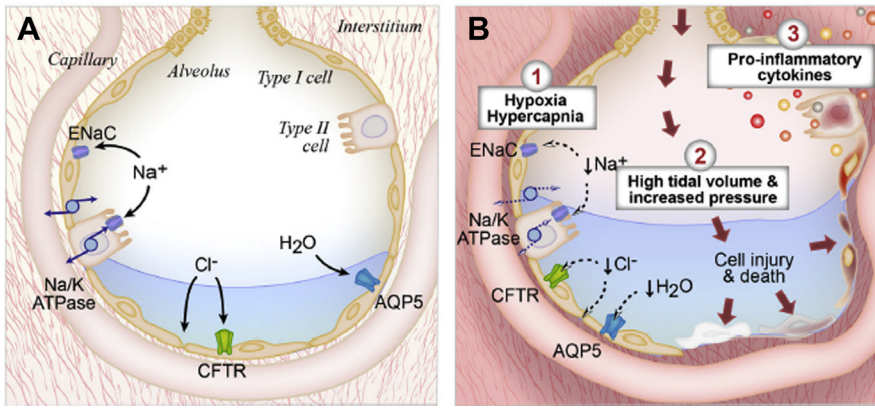


Fig. 5. Alveolar fluid clearance in uninjured lung vs. ARDS. Alveolar fluid clearance pathways in edematous uninjured lungs (*A*) and in ARDS (*B*). Both types I and II alveolar epithelial cells absorb sodium, chloride, and water, respectively, via epithelial sodium channels (ENaCs), cystic fibrosis transmembrane conductance regulator (CFTR), and aquaporin-5 (AQ-5) channels. Energy-dependent Na^+/K^+ ATPase activity on the basolateral membrane of epithelial cells establishes an osmotic driving gradient for movement of sodium from the alveolar space into the interstitium for removal by capillary blood or lymphatic clearance. Chloride follows passively either by CFTR or paracellularly with water moving transcellularly via AQ-5 or paracellularly. Other cation channels not illustrated are also involved. These pathways along with surfactant maintain a dry and compliant alveolar space for efficient gas exchange. With injury to the lung (*B*) and loss of the normal tight alveolar–capillary barrier such as in ARDS, fluid moves into the lungs and is less readily reabsorbed. Hypoxia and hypercapnia cause downregulation and loss of the ion and water channels as well as Na^+/K^+ ATPase activity. This may be compounded by various proinflammatory cytokines and mechanical ventilator-induced lung injury involving high distending volumes and pressures. (*From* Huppert LA, Matthay MA, Ware LB. Pathogenesis of Acute Respiratory Distress Syndrome. Semin Respir Crit Care Med. 2019 Feb; 40(1):31-39; with permission.)

Pathophysiology of Lung Injury from Ventilatory Support in Acute Respiratory Distress Syndrome

An understanding of ARDS physiology, whose key features include gas exchange abnormalities often requiring ventilatory support and atelectasis/decreased compliance with significant regional heterogeneity, has implications for ventilatory support strategies. The role of lung injury while on positive pressure ventilation is the best studied. Positive pressure ventilation along with PEEP reduces the work of breathing and prevents atelectasis of nearly collapsed lung units to improve gas exchange. Furthermore, positive airway pressure helps reduce further edema formation in many edematous states, including the increased alveolar permeability of ARDS.[50] However, as long known, mechanical ventilation also exacerbates the ongoing processes of lung injury and even injury to other critical organs beyond the lung (**Fig. 6**), broadly termed ventilator-induced lung injury (VILI). VILI is often differentiated at the extremes of lung volume[51]; injury at high lung volumes is due to alveolar overdistension (barotrauma/volutrauma), whereas injury at low lung volumes is due to cyclical opening and closing of distal airways and alveoli (atelectrauma). High respiratory rate and inspiratory flow theoretically would increase total stress at both high and low lung volumes, although the effect of these variables within normal clinical ranges on the progression of injury remains uncertain.[52] Other etiologies of VILI include patient self-inflicted lung

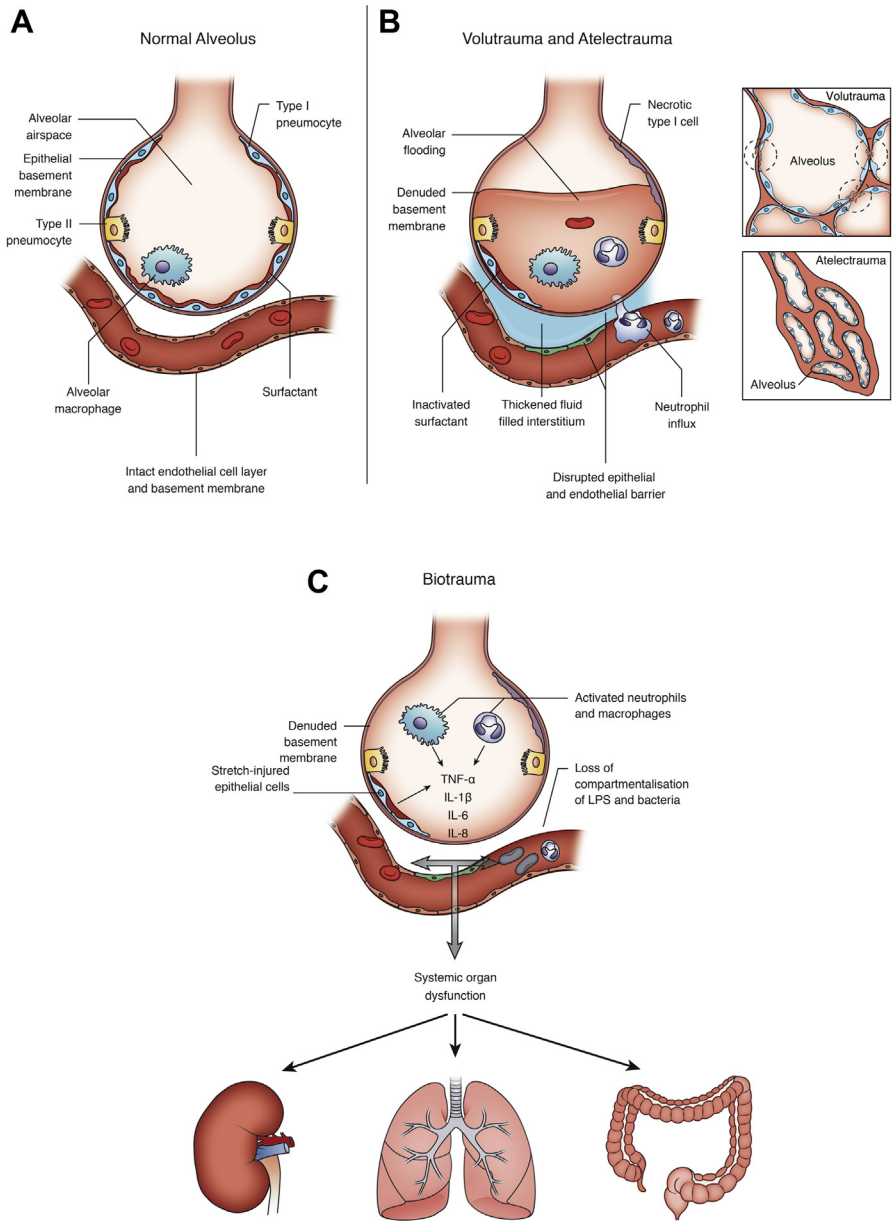


Fig. 6. Events and forms of ventilator-induced lung injury (VILI). The normal alveolus (*A*) is contrasted with the alveolus (*B*) injured by mechanical ventilation by volutrauma and atelectrauma causing endothelial and epithelial injury, greater alveolar–capillary permeability, proteinaceous alveolar edema, and recruitment of inflammatory cells. Activation of resident and recruited cells results in biotrauma (*C*) with the production of proinflammatory mediators that propagate the injury and spillover into the circulation to cause systemic organ damage and dysfunction (*D*). (*From* Curley GF, Laffey JG, Zhang H, Slutsky AS. Biotrauma and Ventilator-Induced Lung Injury: Clinical Implications. Chest. 2016; 150(5): 1109-17; with permission.)

injury (P-SILI) described below, and biotrauma, the downstream local and systemic biological effects of all ventilation-related injury.

Volutrauma, Barotrauma, Atelectrauma, and Biotrauma

Volutrauma and barotrauma represent 2 depictions of the same process, in which excessive mechanical power causes alveolar overdistension and repetitive strain[53] and has been well-described for decades.[54] Clinical strategies to avoid volutrauma and barotrauma, termed lung-protective ventilation, are strongly associated with improved mortality in ARDS.[14] These include targeted tidal volumes of 6 mL/kg ideal body weight, plateau pressures less than 30 cmH_20, driving pressures (plateau pressure—PEEP) < 16 cmH_2O, and judicious PEEP; however, even these goals may not be adequately protective. None allow for delivered tidal volumes to scale with the fraction of nonaerated lung; a more individualized approach would incorporate some measurement of aerated lung volume, such as with nitrogen wash-in/wash-out or helium dilution techniques, or CT quantitation of aerated lung volume.[55]

It is important to note that plateau pressure decreases as the duration of time spent at end-inspiratory occlusion lengthens, likely due to delayed recruitment of additional lung volume via surfactant spread and alveolar pendelluft. Thus, a shorter end-inspiratory occlusion plateau pressure is recommended as a marker of lung injury.[27] Additionally, plateau pressures may not correlate well with transpulmonary pressure, especially if there is significant extrathoracic restriction, such as with severe obesity, ascites, advanced pregnancy, or extensive thoracic burns.[56] Lastly, regional heterogeneity of lung compliance can lead to local overdistension, as visualized on CT, despite global lung-protective ventilation[57]; this likely occurs predominantly in areas of stress concentration. Various bedside techniques, especially electrical impedance tomography (EIT) to noninvasively monitor changes in regional lung ventilation across the transverse plane of the chest, may help tailor ventilatory support to avoid such injury.[58] Gross overdistension and rupture of alveoli can also lead to pneumothorax, pneumomediastinum, and air embolism in ARDS, though this is rare in the age of lung-protective ventilation.

Injury at low lung volumes due to stresses from cyclical opening and closing of alveoli and distal airways, associated with parenchymal shear injury, is collectively termed atelectrauma. Animal models of ARDS demonstrate that cyclical opening and closing of alveolar ducts and even bronchioles (depending on the level of PEEP) leads to site-specific lung injury,[59] which correlates with findings in human lungs on autopsy series.[60] Pressures required to maintain open airways vary depending on patient and lung region but globally can be as high as 13 cmH_20 when monitoring the lower inflection point of the pressure/volume curve.[61] Thus, injury from cyclical atelectasis may be prevented with the application of higher PEEP.[62] Although large trials of high versus low PEEP in ARDS have shown no mortality reduction,[63,64] there are likely patient subsets who might benefit from higher or lower PEEP. Notably, decremental PEEP trials to identify the pressure–volume curve associated with the best dynamic compliance ("open lung strategy") may reduce mortality in ARDS.[65,66] PEEP titration targeting a transpulmonary pressure of 0 to 10 cmH_2O at end expiration using esophageal balloon pressure measurement for estimation of pleural pressure is also promising for optimizing respiratory parameters and reducing overall lung injury.[67] Evaluation of regional recruitability continues to be an active area of investigation; emerging bedside techniques include the multiple pressure–volume curves method[68] and EIT.[58]

The genetic, molecular, and cell biological events of parenchymal stress and strain in all types of VILI are termed biotrauma. It is the cellular response to alveolar and small airway cellular injury with gene transcription and elaboration of numerous

proinflammatory mediators that drive ongoing lung injury and cause systemic organ damage and dysfunction.[52] These processes, mediators, and their effects are more fully presented by other articles in this series.

Patient Self-Inflicted Lung Injury

Afferent signaling to the CNS of impaired gas exchange, lung irritant and stretch receptor activation, and the work of breathing can lead to vigorous injurious respiratory efforts to both diseased and at-risk lung regions even when tidal volumes and plateau pressures are limited.[69] Convincing data come from animal models, in which neurologically-stimulated hyperventilation itself directly induces acute lung injury.[70] It is likely that the effects of P-SILI are most profound on basilar lung units where swings in local intrapleural negative pressure caused by the proximity of the diaphragm are greatest.[71–73]

Most clinical data suggesting P-SILI derive from studies correlating spontaneous breathing efforts during mechanical ventilation with increased mortality. Despite similar tidal volumes and plateau pressures, assisted breaths can lead to worsened lung injury in early ARDS compared to controlled breaths, offering supportive evidence for neuromuscular blockade, especially in the presence of significant patient-ventilator dyssynchrony,[73] but controlled trials have not convincingly demonstrated a mortality benefit.[74] The dangers of spontaneous ventilation on the progression of lung injury must be weighed carefully alongside its beneficial effects in preventing respiratory muscle atrophy and the risks with additional sedation or neuromuscular blockade to abrogate spontaneous efforts.[75]

PATHOPHYSIOLOGY OF COVID-19 LUNG INJURY

The SARS-CoV-2 pandemic beginning in early 2020 has caused millions of deaths from severe COVID-19 lung injury and respiratory failure, often complicated by multisystem injury. While infection can present in myriad ways, SARS-CoV-2 is largely transmitted by aerosolization and typically causes symptoms of fatigue, malaise, fever, cough, sore throat, and dyspnea from pneumonitis, hypoxemia, and respiratory failure. People of all ages and backgrounds are afflicted. Risk factors for poorer outcomes include older age, obesity, male sex, diabetes, hypertension, cardiovascular disease, smoking, cancer, autoimmune disorders, and other chronic diseases. Those with limited reserve, particularly in lung function, have the worst prognosis. While COVID-19 has been described as an atypical form of ARDS, the issue remains highly controversial, as pathophysiologic similarities with ARDS from other causes outnumber any differences (**Table 1**). In many ways, the advent of COVID-19 as a trigger for ARDS has reopened many questions on the pathophysiology of ARDS itself.

Pathogenesis of COVID-19 Lung Injury

The pathogenesis of COVID-19 lung injury involves direct viral damage and a host defense response with thrombotic and inflammatory reactions in the lung and elsewhere.[76] The alveolar epithelium and vascular endothelium express angiotensin-converting enzyme 2 (ACE-2), to which the virus attaches and then is internalized along with the membrane-bound ACE-2. Consequently, cellular damage ensues and evolves to interstitial edema and alveolar fluid filling, similar to the process of alveolar flooding in ARDS. Autopsy data, reflecting advanced disease, reveal typical ARDS features, including exudative proliferative and fibrotic phases of diffuse alveolar damage, hyaline membranes, alveolar and interstitial edema, atypical pneumocyte hyperplasia, alveolar hemorrhage, infarction, endothelial cell injury, and capillary congestion with microthrombosis and dilation.[77,78] Notably, there is greater vasculopathy,

Table 1
Comparisons between pathophysiology of COVID-19 lung injury and acute respiratory distress syndrome

	COVID-19 Lung Injury	Acute Respiratory Distress Syndrome
Onset	8–12 d	< 7 d (Berlin definition)
Cause	SARS-CoV-2 (agent of COVID-19) via direct viral and immune response-mediated-injury	Multiple pulmonary and nonpulmonary (systemic) causes, both infectious and noninfectious
Histologic features	• DAD • Organizing pneumonia • More severe vasculopathy - Thromboembolism - In situ microthrombi - Capillary dilatations - Endothelial damage	• DAD - Exudative phase - Proliferative phase - Fibrotic phase • Vascular changes - Thromboembolism - In situ microthrombi - Capillary dilatations - Endothelial damage
Imaging	• Peripheral and basilar ground-glass opacities in early disease • Progression to typical consolidation as in ARDS	• Consolidations, often patchy and dependent
Respiratory mechanics	• C_{ST} range: 20–90 mL/cmH_2O • Compliance and oxygenation often improved with increased PEEP or prone positioning	• C_{ST} range: 10–78 mL/cmH_2O • Compliance and oxygenation often improved with increased PEEP or prone positioning
Pulmonary vasculature	• Mild-moderate pulmonary hypertension • Unknown whether HPV intact or impaired • Vasculature responsive to almitrine and inhaled NO	• Mild-moderate pulmonary hypertension • HPV intact • Vasculature responsive to almitrine, calcium channel blockers, nitrates, PDE-5 inhibitors, and inhaled NO
Gas exchange	V_A/Q mismatching: • Hypoxemia due to low V_A/Q and shunt • No evidence for diffusion limitation • Hypercapnia due to permissive hypoventilation, and all forms of V_A/Q mismatch	V_A/Q mismatching: • Hypoxemia due to low VA/Q and shunt • No evidence for diffusion limitation • Hypercapnia due to permissive hypoventilation, and all forms of V_A/Q mismatch
Alveolar epithelial fluid clearance	Likely reduced due to alveolar type I and II cell damage, but not formally tested	Reduced due to alveolar type I and II cell damage; unresponsive to beta-adrenergic therapy

Abbreviations: ARDS, acute respiratory distress syndrome; C_{ST}, static compliance; COVID-19, coronavirus disease-2019; HPV, hypoxic pulmonary vasoconstriction; NO, nitric oxide; PDE-5, phosphodiesterase-5; PEEP, positive end-expiratory pressure; V_A/Q, alveolar ventilation–perfusion ratio.

including macro- and microthrombosis, endothelial cell injury, vascular dilation, and aberrant angiogenesis[77,79] in COVID-19 and the earlier SARS injury than with H1N1 influenza and ARDS.[80] However, lung biopsies in early COVID-19[81–83] do not show the marked vascular pathology noted at autopsy. Limited bronchoalveolar lavage data demonstrate a more monocytic and lymphocytic predominance in the airspace

typical of viral pneumonias[84] compared with the dominantly neutrophilic cell population in ARDS.[85] Understanding the respiratory pathophysiology of COVID-19 lung injury and ARDS is fundamental to better clinical care and support.

Lung Compliance and Respiratory Mechanics

A possible unique ARDS presentation was reported by Gattinoni and colleagues (2020) and followed up with a larger study of 32 patients[86] with potential implications for physiologic support.[87] In these studies, a small fraction (<20%) had "near normal" static total respiratory system compliance (C_{ST}) of 70 to 90 mL/cmH_2O with an average of 50 (**Fig. 7**) compared with an average of 40 in series of ARDS patients.[88] On the basis of a slightly higher average C_{ST} observed in earlier ARDS patients, they proposed a controversial high compliance L phenotype (L for low elastance, low PEEP recruitability, and more dominant low V_A/Q gas exchange abnormality than shunt) combined with vasoplegia and loss of HPV. Nonetheless, many patients continue to worsen, suggesting only a temporal sequence of early disease evolving to more classic ARDS pathophysiology. A small fraction of patients with higher compliance of the L phenotype has been described in equal proportions in subsequent series.[89–93] This is neither unique to COVID-19, as shown in ARDS before the pandemic,[93–95] nor to patients with other influenza pneumonias requiring mechanical ventilation.[96]

Several explanations for better compliance early in COVID-19 lung injury and even in ARDS are possible. The first is the predominantly peripheral and basilar ground-glass opacities (GGO) very prevalent on CT imaging (**Fig. 8**) early in the course of the disease.[97,98] While never directly studied, GGOs, by virtue of their lesser CT density than consolidations, could be more compliant. This is suggested indirectly in patients when dynamic (but not static) compliance was measured and surprisingly correlated with the volume of CT-defined GGO, in contrast to a negative correlation with

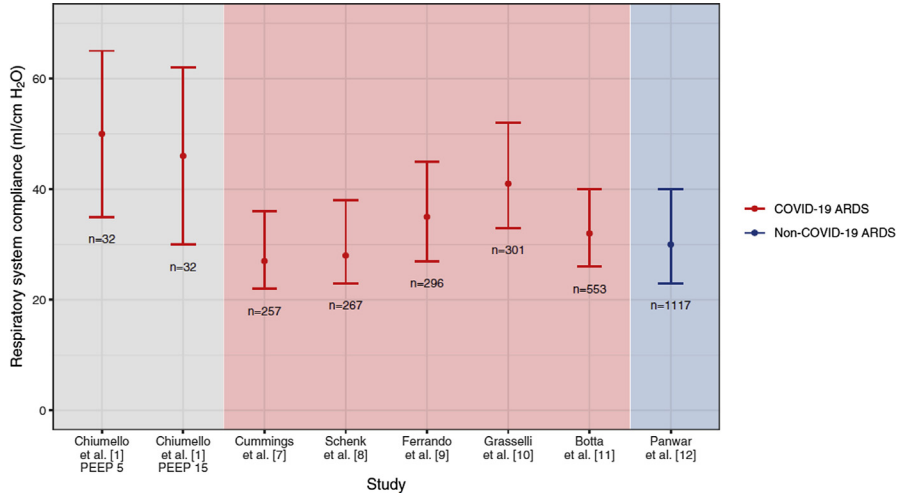


Fig. 7. Respiratory system compliance in COVID-19 and non-COVID-19 ARDS. Distribution of respiratory system compliance (C_{ST}) values in various studies of patients with COVID-19 lung injury and compared with patients with ARDS. Most studies find no significant differences between the 2 forms of lung injury. (*From* Goligher EC, Ranieri VM, Slutsky AS. Is severe COVID-19 pneumonia a typical or atypical form of ARDS? And does it matter? Intensive Care Med. 2021;47(1):83-85. doi:10.1007/s00134-020-06320-y; with permission.)

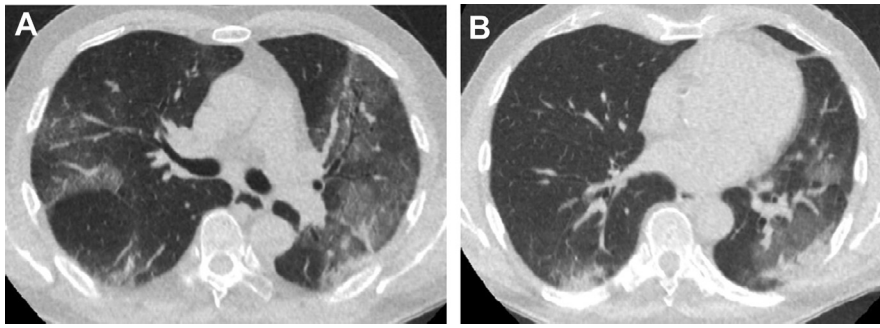


Fig. 8. Representative CT imaging of early COVID-19 lung injury. Two axial slices of a patient with COVID-19 lung injury at presentation to the emergency department after several days of fever, mild dyspnea, cough, and malaise. The images show multiple areas of typical ground-glass opacities and some early consolidation (*A*, *B*). (*From* Schalekamp S, Bleeker-Rovers CP, Beenen LFM, Quarles van Ufford HME, Gietema HA, Stöger JL, Harris V, Reijers MHE, Rahamat-Langendoen J, Korevaar DA, Smits LP, Korteweg C, van Rees Vellinga T, Vermaat M, Stassen PM, Scheper H, Wijnakker R, Borm FJ, Dofferhoff ASM, Prokop WM. Chest CT in the Emergency Department for Diagnosis of COVID-19 Pneumonia: Dutch Experience. Radiology. 2020: 203465; with permission.)

consolidated lung.[99] Surfactant producing AE type II cells express ACE-2 and contain almost 50% of total lung surfactant.[100] With injury and release of these stores, the compliance decline expected with microvascular leakage might be buffered, but only temporarily before surfactant inactivation occurs and production ceases. Hyaluronan, also produced by AE type II cells[101] as part of the alveolar glycocalyx, enhances surfactant function and reduces fluid accumulation;[102] in early injury before excessive accumulation occurs, it may limit surfactant inactivation.[103,104]

Several other aspects of compliance in ARDS and COVID-19 lung injury warrant discussion. The idea that a more vascular type injury may lead to better-than-expected compliance[99] runs counter to the fact that poorly perfused or nonperfused lung regions become stiffer by hypocapnic pneumoconstriction and then by cessation of surfactant production.[105] This normal V_A/Q matching mechanism based on responses to changes in local blood-borne CO_2 delivery redirects ventilation from poorly perfused regions to those with greater blood flow. Several studies have in fact found no correlation between the amount of affected lung by CT imaging and C_{ST}.[106–108] It should also be pointed out that initial higher compliance is a poor predictor of risk and progression to severe lung injury in ARDS.[109]

Pulmonary Hemodynamics and Vascular Regulation

One proposed aspect of COVID-19 lung injury is vasoplegia and loss of HPV that may even result in paradoxic hyperperfusion. CT imaging of the vasculature shows large and small vessel dilations in areas of affected lung and dual-energy CT perfusion imaging (**Fig. 9**) reveals greater perfusion, particularly in GGO areas, supporting the possible idea of vasoplegia and dysregulated perfusion.[99,110] Estimated PA pressures by transesophageal echocardiography in severe COVID-19 lung injury show only modest elevations[111,112] as in ARDS.[113,114] This has now been corroborated with right heart catheterization data in 21 mechanically ventilated patients, showing mild pulmonary hypertension (mean PAP—27 mm Hg, PVR—1.6 Woods units, and cardiac output—7.3 L/min).[115] These data do not rule out pulmonary hypertension (PH) in some with COVID-19 lung injury as there are case reports of right heart dysfunction

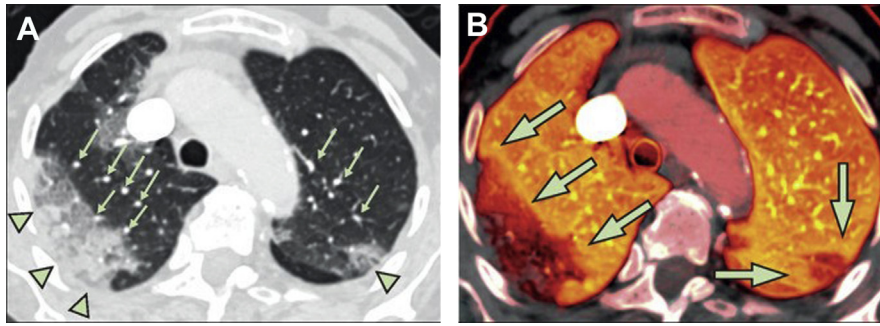


Fig. 9. Changes in pulmonary vascular anatomy in focal COVID-19 lung disease. Conventional (*A*) and dual-energy CT (*B*) in a patient with COVID-19 pneumonia without evidence of pulmonary emboli. (*A*) There is a large area of peripheral ground-glass opacity and consolidation within the right upper lobe and smaller ground-glass opacity in the posterior left upper lobe (green *arrowheads*), which are accompanied by dilated subsegmental vessels proximal to, and within, the opacities (green *arrows*). (*B*) The accompanying image of pulmonary blood volume shows corresponding wedge-shaped areas of decreased perfusion within the upper lobes, with a peripheral halo of higher perfusion (green *arrows*). (*From* Lang M, Som A, Mendoza DP, et al. Hypoxaemia related to COVID-19: vascular and perfusion abnormalities on dual-energy CT. Lancet Infect Dis. 2020;20(12):1365-1366. doi:10.1016/S1473-3099(20)30367-4; Reprinted with permission from Elsevier.)

and cor pulmonale consistent with either PH or viral myocardial injury.[116] At this time, all analyses of pulmonary hemodynamics are complicated by the likelihood of wide regional PVR differences such that vascular beds with low resistance and possible lack of HPV are counterbalanced by other areas of higher resistance due to obstruction from pulmonary embolism and/or in situ thrombosis, as observed in over 30% of patients despite anticoagulant prophylaxis.[117] Loss of ACE-2 activity from internalization with the virus will result in less breakdown of vasoconstricting angiotensin II to its vasodilating and antiinflammatory metabolite Ang1-7.[118] In addition, bradykinin and some of its active edema-promoting metabolites are elevated in COVID-19, several of which are metabolized by ACE-2.[119]

If HPV is blunted or absent, multiple mechanisms may be responsible. Reductions in alveolar P_{CO_2} will blunt HPV.[22] Another possibility is that SARS-CoV-2 may cause changes in proteins involved in vascular O_2 sensing.[120] Finally, viral-mediated alveolar–capillary endothelial cell injury[77,79,121,122] may impair alveolar hypoxia sensing and transduction to the vascular smooth muscle.[123] Another explanation, unrelated to the above possible viral-mediated effects, is that those with hypoxemia out of proportion to the extent of lung involvement may have intrinsically blunted HPV at the low end of the wide 5-fold variation in this response among healthy persons.[22] It remains unknown whether HPV is altered in COVID-19 lung injury because to do so would require brief testing with inspired hypoxic gas. As in ARDS, almitrine improves gas exchange in patients with COVID-19 lung injury,[124] as does inhaled nitric oxide.[125] However, because these drugs also alter PVR in normoxia,[126–128] they are not wholly ideal to evaluate HPV and thus do not clearly establish an alteration in HPV in patients with COVID-19 lung injury.

Causes of Hypoxemia, Hypercapnia, and Dyspnea in COVID-19 Lung Injury

There have been alarming reports of what has been termed silent hypoxemia or happy hypoxia, denoting marked arterial hypoxemia despite an apparent lack of dyspnea in otherwise conscious and spontaneously breathing patients. Delirium associated with

the infection may increase the presentation of silent hypoxemia.[129] The diagnosis of possible silent hypoxemia varies from a small minority of patients to as many as one-third when assessed simply as the absence of dyspnea.[89,90,130–132] The hypoxemia can be profound, with values of SpO_2 and Pa_{O_2} as low as 70% and 40 mm Hg,[133] yet surprisingly in the half-century since the description of ARDS, silent hypoxemia has never been reported before. In reviews of ARDS, a few patients have presented without dyspnea, but no percentages are given and none in relation to the degree of severe hypoxemia.[85] In severe viral-induced ARDS, including SARS-CoV-1 and H1N1 influenza infection, those requiring oxygen without dyspnea ranged from 0% to 27%,[109,134–136] suggesting this phenomenon is virally-mediated. In a recent analysis of prehospitalized patients, the average SpO_2 divided by respiratory rate was 5.0 in March 2020, compared with 3.2 to 3.5 in March of the preceding 3 years, suggestive of more silent hypoxemia and less tachypnea in the COVID-19 era.[137]

Hypoxemia in COVID-19 as described in ARDS is caused by low ventilation-to-perfusion (V_A/Q) mismatching and shunt. In ARDS, there is no evidence for diffusion limitation, but this has not yet been studied in COVID-19 lung injury using MIGET. Recently, detection of small bubbles with intravenous injection by transcranial Doppler correlated with hypoxemia and reduced compliance in patients with COVID-19 lung injury and was attributed to diffusion limitation due to microvascular dilations noted at autopsy.[138] However, normally occurring intrapulmonary arteriovenous anastomoses of similar diameters causing equal bubble scores in healthy people do not cause hypoxemia.[139] Modeling of early COVID-19 lung injury is conflicting. One study suggests the reported hypoxemia severity in early disease can be reasonably explained by a combination of pulmonary embolism, V_A/Q mismatching in noninjured lung regions from redirection of blood flow from obstructed regions, and normal perfusion of the relatively small fraction of injured lung and does not require the loss of HPV, hypoxic vasodilation, or diffusion limitation.[140] Another finds that the L-type phenotype can only be explained by hyperperfusion of collapsed lung regions, loss of HPV, extensive microvascular obstruction, and diffusion limitation in affected areas.[141] Hypercapnia also develops in very severe COVID-19 lung injury for the same reasons as described earlier in the section on ARDS. As in ARDS, the entire spectrum of V_A/Q mismatching contributes to the CO_2 dead space calculation. Reported values of dead space as high as 75% in COVID-19 lung injury[142] due largely to vascular obstruction would be inconsistent with the mild PH and preserved cardiac output in most patients as noted above.

The absence of respiratory distress in some patients with COVID-19 lung injury include better-than-expected lung compliance (discussed above) with arterial hypocapnia in those that can increase ventilation sufficiently to partially blunt dyspnea arising from hypoxemia and other stimuli from the injured lung and elsewhere in the body. Furthermore, there is speculation that neural infection by SARS-CoV-2 (given the presence of ACE-2 in the carotid body[143] and elsewhere in the CNS[144]) leads to a loss of normal perception of increased breathing from hypoxemia, lung irritant and stretch receptor activity, respiratory muscle effort, fever, anxiety, sympathetic nervous system activation, increased metabolism, and metabolic acidosis. Other coronaviruses infect the brainstem via viral transmission along afferent nerves arising in the lung, nasopharynx, and other peripheral mechanoreceptors and chemoreceptors.[145] Regarding the respiratory muscles, they express ACE-2 and can develop myopathic changes with infection that might lessen afferent signaling of their effort.[146]

Control of ventilation and dyspnea perception is complex.[147] Afferent signals to the brain regarding breathing and its perception (**Fig. 10**) include (a) chemoreception by

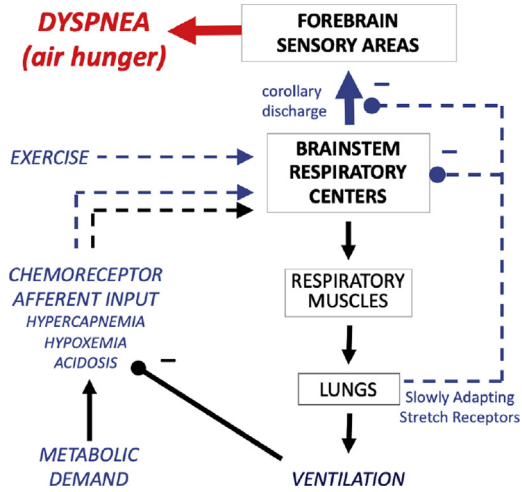


Fig. 10. Signaling pathways in the control of ventilation. Schematic representation of the multiple afferent signaling pathways to the brainstem respiratory centers that control ventilation from mechano-stretch receptors in muscles and joints, irritant and stretch receptor in the lungs, arterial P_{O_2} and P_{CO_2} (from peripheral chemoreceptors in the carotid body, arterial pH and P_{CO_2} (from central chemoreceptors in the brainstem), fear, and emotional and pain stimuli from the hypothalamus. Signals from the brainstem are also conveyed (corollary projection) to the conscious regions of the brain (amygdala and insular cortex) that perceive dyspnea, work of breathing, and respiratory distress. In COVID-19, it is proposed that some of this signaling and cortical perception may be impaired by direct viral injury to these pathways. (*From* Simonson T, Baker T, Banzett R, et al. Silent hypoxaemia in COVID-19 patients. J Physiol 2021;599(4):1057-1065. doi:10.1113/jp280769; with permission.)

peripheral and central chemoreceptors of arterial P_{O_2}, pH, and P_{CO_2} and (b) signaling from the lungs, respiratory muscles, and chest wall to the brainstem respiratory control center and its "corollary projection" to higher cortical centers in the anterior insular cortex and amygdala, where the conscious sensation of breathing resides.[148] Signaling from peripheral and central chemoreceptors in response to arterial P_{CO_2} and P_{O_2} changes, like that of HPV,[22] varies 5-fold to 10-fold among individuals[149,150] and is lower in older and patients with diabetes.[133] In addition to interindividual variability of hypoxic ventilatory response (HVR), a similar high variability exists with the symptomatic dyspnea threshold onset during hypoxemia, with an observed threshold range of end-tidal P_{O_2} from 35 to 60 mm Hg in healthy subjects maintained eucapnic at a fixed ventilation that likely correlates with HVR.[151]

Whatever the pathophysiologic underpinnings of silent hypoxemia, it represents a significant threat for patients sent home with mild COVID-19 and told to seek care only when they become dyspneic or sicker. The fate of many with silent hypoxemia is one of eventual deterioration and death. It can be reasonably argued that many hours and days of severe unrecognized hypoxemia exact a multi-organ toll that if prevented sooner might improve outcomes because severe hypoxemia itself, in conjunction with systemic inflammation in COVID-19, contributes to further lung damage via exacerbation of local inflammatory injury.[152] Additionally, hypoxemia may contribute to hypercoagulability and thrombosis in the lung and other organs.[153] Hypoxia-inducible factor-1 is increased in response to hypoxemia and in an animal model of herpes virus infection was shown to increase viral replication.[154]

Treatment Strategies for COVID-19 Lung Injury

As already discussed, the numerous published large series of patients with COVID-19 lung injury and respiratory failure find little difference in many of the usual respiratory parameters of compliance, driving pressure, PEEP, V_A/Q mismatching, and shunt seen in ARDS. Accordingly, most physicians have employed low tidal volume ventilation with permissive hypercapnia, prone positioning, intermediate levels of PEEP, neuromuscular blockade, and conservative fluid therapy, in addition to pharmacologic therapies specific for COVID-19 as supportive data emerged. The concern raised for patients with the L type phenotype being harmed by smaller tidal volumes and higher PEEP has never been subjected to rigorous clinical trial, and the improving survival rates of patients with severe COVID-19 to that with standard ARDS support suggests that harms of greater PEEP with overdistension and injury of more compliant lung (VILI) and hemodynamic compromise have not been realized.

Nonetheless, some aspects of COVID-19 have stimulated considerations of therapies either tried and found unsuccessful in ARDS or novel possibilities based on the pathophysiology of the injured lung in COVID-19. These include inhaled nitric oxide to improve V_A/Q matching and reduce shunt by pulmonary vasodilation only in ventilated areas as well as possible direct viral killing and antiinflammatory effects. Other forms of inhaled vasodilators including prostacyclin and its analogs are being used. Enhancement of HPV with almitrine in affected areas in the few countries where this is available has had success in improving oxygenation. The recent success with dexamethasone and in ARDS[155] may be multifactorial beyond suppression of inflammation to include stimulation of fluid absorption, surfactant secretion, and reduction in HPV.[156] Studies are underway to test whether the prominent hypercoagulopathy of COVID-19 may require higher dosing of standard prophylactic anticoagulants. The critical role of ACE-2 and its role in setting the balance of the renin–angiotensin system offers the possibility of using Ang1-7 to reduce inflammation and reduce vasoconstriction.[157]

SUMMARY

The pathophysiology of ARDS and COVID-19 lung injury share many of the same aspects of reduced lung parenchymal compliance, vasculopathy, alveolar flooding, and gas exchange impairment arising from direct infectious causes and noninfectious injuries. Exuberant host defense inflammatory responses lead to endothelial and epithelial cell damage and loss of the normally tight alveolar–capillary barrier and its ability to maintain a dry alveolar space for efficient gas exchange. The heterogenous regional extent of injury creates stress factors on surrounding lung that can further propagate injury with mechanical ventilation and possibly with vigorous spontaneous breathing efforts. While there may be some differences between ARDS and COVID-19 lung injury in aspects of lung compliance, pulmonary vascular responses, and hypoxia sensing and responses that underlie the phenomenon of silent hypoxemia, there remains considerable dispute as to whether they really are distinguishing and important enough to warrant different strategies of care. The pathophysiologic features of both lung injuries have important ramifications for life-sustaining supportive care, and it is hoped that pharmacologic therapies may reduce mortality and enhance functional outcomes.

CLINICS CARE POINTS

- COVID-19-related lung injury should be managed using the same principles of lung-protective ventilation proven efficacious in classic ARDS.

- The degree of heterogeneity seen in parenchymal injury in both classic ARDS and COVID-19-related lung injury supports the use of early proning in severe or rapidly-deteriorating patients to limit ongoing stress concentration and propagation.
- Treatments that improve hypoxemia via ventilation–perfusion matching without addressing ongoing mechanical stresses on lung parenchyma, such as inhaled vasodilators, may temporize refractory hypoxemia but are unlikely to alter the course of disease in ARDS.
- Avoidance of significant patient-ventilator dyssynchrony during the progression of lung injury may limit further injury from P-SILI.
- Hypoxemia and pulmonary infiltrates in the absence of respiratory distress or impaired compliance appear to be common in early COVID-19-related lung injury and do not preclude the development of progressive respiratory failure seen in classic ARDS.

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