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REVIEW

Understanding the pathophysiology of typical acute respiratory distress syndrome and severe COVID-19

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ABSTRACT

Introduction: Typical acute respiratory distress syndrome (ARDS) and severe coronavirus-19 (COVID-19) pneumonia share complex pathophysiology, a high mortality rate, and an unmet need for efficient therapeutics.

Areas covered: This review discusses the current advances in understanding the pathophysiologic mechanisms underlying typical ARDS and severe COVID-19 pneumonia, highlighting specific aspects of COVID-19-related acute hypoxemic respiratory failure that require attention. Two models have been proposed to describe the mechanisms of respiratory failure associated with typical ARDS and severe COVID-19 pneumonia.

Expert opinion: ARDS is defined as a syndrome rather than a distinct pathologic entity. There is great heterogeneity regarding the pathophysiologic, clinical, radiologic, and biological phenotypes in patients with ARDS, challenging clinicians, and scientists to discover new therapies. COVID-19 has been described as a cause of pulmonary ARDS and has reopened many questions regarding the pathophysiology of ARDS itself. COVID-19 lung injury involves direct viral epithelial cell damage and thrombotic and inflammatory reactions. There are some differences between ARDS and COVID-19 lung injury in aspects of aeration distribution, perfusion, and pulmonary vascular responses.

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1. Introduction

According to the current Berlin definition, acute respiratory distress syndrome (ARDS) is characterized by refractory hypoxemia, respiratory failure not explained by cardiac failure or fluid overload, and bilateral opacities on chest imaging, presenting within 1 week of a known clinical insult or worsening respiratory symptoms [1]. Several definitions of severe COVID-19 pneumonia have been proposed by health-care institutions; recognized criteria include dyspnea, peripheral oxygen saturation below 93%, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mmHg, and/or bilateral infiltrates involving more than 50% of the lung fields on chest radiographs [2,3]. Infiltrates are typically bilateral in severe COVID-19 and continuous positive airway pressure or positive end-expiratory pressure (PEEP) levels ≥5 cmH_2O are often applied; therefore, most patients with severe COVID-19 pneumonia fulfill the clinical criteria for ARDS.

However, since the early phases of the pandemic, several specific pathophysiologic traits have been highlighted in COVID-19. These include severe endothelial injury [4], hypoxemia not fully explained by loss of aeration [5,6], alveolar-capillary microthrombi [7], venous thromboembolism [8], and marked inflammatory response [9] with possible multisystemic involvement [10]. A broad scientific debate is ongoing on whether these features should modify our clinical approach to COVID-19-related respiratory failure, compared with the conventional protocols applied in classic ARDS, in particular with regard to noninvasive [11] and invasive respiratory support [5,12]. Overall, whereas ARDS is a clinical syndrome including various causes of pulmonary and extrapulmonary injury, COVID-19 pneumonia is a single disease with two specific concurring mechanisms of lung damage: direct viral insult and host local as well as systemic inflammatory response [13,14].

This review does not enter the long-standing discussion of whether COVID-19 pneumonia should or should not be considered ARDS or a distinct disease, but instead highlights the specific aspects of respiratory failure related to COVID-19, thus considering severe COVID-19 pneumonia as a subphenotype of ARDS. In fact, while several disease-specific features can be observed in COVID-19, severe COVID-19 pneumonia clearly fulfill the current clinical

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Article highlights

- ARDS is a clinical syndrome with different causes leading to complex biological and clinical heterogeneity.
- Although a single definition of ARDS is widely used and accepted, the heterogeneity of ARDS has been associated with negative treatment outcomes with pharmacotherapies.
- The pathogenesis of COVID-19 lung injury involves direct viral epithelial cell damage and a host defense response with thrombotic and inflammatory reactions in the lung.
- There are some differences between ARDS and COVID-19 lung injury in aeration distribution, perfusion, and pulmonary vascular responses.
- Further research is warranted to identify sub-phenotypes of ARDS, including severe COVID-19 pneumonia, that could benefit from specific treatments and ventilatory strategies.

criteria for ARDS. The aim of this review is to summarize the current advances in understanding the pathophysiological mechanisms underlying typical ARDS and COVID-19, highlighting peculiar aspects of COVID-19-related acute hypoxemic respiratory failure that might require a clinician's attention.

2. Pathophysiology of typical ARDS

ARDS can originate from a variety of heterogeneous conditions in which the pathophysiologic pathways converge on a single anatomic structure, namely the alveolar-capillary barrier, causing diffuse alveolar damage (DAD) [15]. Two distinct components form the alveolar-capillary barrier: the alveolar epithelium and the capillary endothelium, interleaved by the interstitium, organized in a complex extracellular matrix scaffold [16]. The key aspects of ARDS and COVID-19 pneumonia are summarized in Table 1.

2.1. Differences between pulmonary and extrapulmonary ARDS

Studies on ARDS have explored the hypothesis that, at least in the earlier phases of the syndrome, pathogenic insults reaching the barrier from either the alveolar or the capillary side could result in different alterations and consequently into diverse clinical presentations of ARDS [17]. This led to the definition of two macro-categories of ARDS: (1) ARDS due to direct pulmonary injury (pulmonary ARDS or ARDSp) and (2) ARDS secondary or indirect or extrapulmonary lung injury (extrapulmonary ARDS or ARDSexp) [17]. Causes of ARDSp include bacterial or viral pneumonia, aspiration pneumonia, lung contusion, and drowning; ARDSexp can be secondary to sepsis, polytrauma, acute pancreatitis, massive blood transfusion, and hemorrhagic shock [18]. From this perspective, the evolution of the ARDS definitions reflects three phases of research and understanding of the disease. Early reports mainly focused on ARDSexp [19], the following decades focused on the possible differences between ARDSp and ARDSexp [17,20], and in the era between the Berlin definition and the COVID-19 pandemic, the distinction between the two was underexplored and a unifying approach was attempted, regardless of the type of pulmonary injury.

Primary insults in ARDSp act primarily on the alveolar epithelial cells, causing fluid leakage and alveolar flooding, further worsened by impaired clearance of edema from the alveolar space [21]. Damage to type II epithelial cells decreases the production of surfactant, and a proliferation of fibroblasts and deposition of the extracellular matrix might constitute the basis for the development of fibrosis, especially when epithelial repair mechanisms are impaired [22,23]. Compared with ARDSexp, ARDSp is characterized at the alveolar level by increased damage to the alveolar epithelium (type I and type II cells), with prevalent alveolar and apoptotic neutrophils, and a marked alveolar increase in inflammatory mediators; at the interstitial space level, by lower interstitial edema, increased cell

Table 1. Key radiological, clinical, and histological findings in ARDSexp, ARDSp, and COVID-19 pneumonia.

	ARDSexp	ARDSp	COVID-19, early	COVID-19, severe
Computed tomography findings				
Ground-glass lesions	+ patchy	–	++ multi-focal, sub-pleural	++
Non-aerated tissue	+ dorsal	++	–	+ dorsal/caudal
Perfusion				
Ventral–dorsal distribution	Bell-shaped	Bell-shaped, dependent on distribution of non-aerated tissue	Dependent on distribution of ground-glass lesions	Decreasing along the ventral–dorsal axis
Diffuse (micro)thrombosis	+	+/–	+/–	++
Increased dead space	++	+	–	++
Non-aerated/non-perfused regions	Unknown	Unknown	–	+
Histology				
Type I and type II epithelial cell lesions	+	++	+	++
Endothelial cell lesions	++	+	+	++
Alveolar neutrophils	±	++	+	++
Alveolar cytokines	+	++	+	++
Collagen fibers	+	+	±	Variable (–/++)
Systemic inflammatory markers	++	±	+/–	++

ARDSexp = extrapulmonary acute respiratory distress syndrome; ARDSp = pulmonary acute respiratory distress syndrome.

infiltration and fibrosis and normal elastic fibers; an increase in inflammatory mediators in the blood less than that observed in sepsis [20,24]. Circulating inflammatory mediators cause indirect injury in ARDSexp, reaching the lungs from the pulmonary endothelial cells, which are the initial target of damage in this type of ARDS [25]. Autopsy studies found higher amounts of alveolar collapse, alveolar wall edema, and fibrinous exudate in ARDSp compared with ARDSexp [26]. Respiratory mechanics parameters might be different in these two forms of ARDS. Despite comparable respiratory system compliance, in ARDSp, lung compliance is decreased, whereas reduction in chest wall compliance predominates in ARDSexp [17]. An early report estimating recruitment based on pressure–volume curves reported a lower potential for recruitment in ARDSp compared with ARDSexp, suggesting a potential role for higher PEEP ventilation strategies in the latter group [27]. The findings of this study were not confirmed in a larger population, thus questioning the actual indication of setting PEEP based on the cause of ARDS [28]. Moreover, a recent meta-analysis with meta-regression did not observe an association between the effect on mortality of higher PEEP strategies and the percentage of patients with ARDSp versus ARDSexp in randomized controlled trials [29]. However, a randomized trial observed that patients with focal ARDSp receiving higher PEEP strategies had higher mortality [30], highlighting how misclassification of patterns of ARDS might be common and possibly have negative consequences on outcomes.

The clinical distinction between ARDSp and ARDSexp is often complex in the real world for two reasons [20]: (1) patients with initial pulmonary damage might evolve from a typical ARDSp pattern to a mixed clinical presentation due to overlapping sepsis and systemic inflammation and (2) coexistence of multiple mechanisms of lung injury in critically ill patients is common. These difficulties might explain why a large meta-analysis including more than 4000 patients did not observe differences in mortality between ARDSp and ARDSexp [18]. Although the American-European Consensus Conference on ARDS definition still recognized potential differences in the clinical management of patients with ARDSp compared to ARDSexp [31], such distinction was abandoned in the current Berlin definition, implying that all patients could possibly benefit from a standardized approach regardless of the cause of ARDS [1]. This unifying approach received criticisms [32], and the numerous disease-specific features identified during the ongoing COVID-19 pandemic further questioned whether a one-for-all approach was feasible [33]. Based on the available evidence, the distinction between ARDSp and ARDSexp might not translate into different therapeutic strategies, also due to the frequent overlap between the pathophysiological and clinical patterns of the two conditions. Nonetheless, the different pathophysiological mechanisms underlying ARDS should be considered when tailoring treatment of these patients. In fact, the current Berlin definition, while proposing a convenient framework to provide general recommendations on respiratory management of ARDS patients, might miss several disease-specific aspects which could influence the treatment in peculiar sub-groups of patients [33].

2.2. Inflammatory phenotypes in typical ARDS

In the last decade, researchers have attempted to identify specific subphenotypes of ARDS to guide mechanical ventilation settings and pharmacological treatments [34]. Recently, the existence of a hyper-inflammatory and a hypo-inflammatory phenotype of ARDS has been proposed [35]. Although several features of the hyper-inflammatory phenotype overlap with characteristics of ARDSexp, the classification is based on a subset of objective clinical variables, including biomarkers of inflammation, coagulopathy, and endothelial injury [36,37] rather on a subjective classification of the cause of ARDS. The hyper-inflammatory, compared to the hypo-inflammatory phenotype, is characterized by higher interleukin-6, interleukin-8, tumor necrosis factor levels while lower protein C levels and PaO_2/FiO_2 ratio [36]. These differences can be observed at ICU admission and tend to remain stable over time [38]; moreover, mortality is consistently higher across studies in the hyper-inflammatory phenotype [36–38]. These phenotypes, currently under investigation, showed different responses to higher PEEP strategies [37], liberal versus restrictive fluid regimens [39], and anti-inflammatory therapies [40]. Although still experimental, this approach based on clustering reflects the need for sub-classifications of ARDS capable of predicting response to individualized treatments and will be extensively investigated in the near future.

3. Pathophysiology of severe COVID-19

As illustrated in Figure 1, the pattern of COVID-19 pneumonia evolves from early to advanced phases. In the early phases of the disease, the predominant findings are single or multiple ground-glass lesions, which may evolve into complete loss of aeration and the appearance of non-aerated tissue [5,6]. Severe COVID-19 pneumonia often requires invasive mechanical ventilation and appears to be a specific phenotype of ARDS (ARDSp), with a distinct histological pattern compared with ARDSexp. Autopsy studies on COVID-19 have reported diffuse alveolar damage, alveolar flooding with the presence of fibrin and hyaluran [41], intense remodeling [42], platelet–fibrin microthrombi [43], and early fibrotic evolution [44], with variable deposition of collagen fibers [45]. Despite several similarities with conventional ARDSp, which is characterized by normal endothelium, COVID-19 pneumonia, despite being a pulmonary ARDS, presents in the early stages with endothelial injury and dysfunction induced by direct viral action and host inflammatory response [46]. In addition to this peculiar mechanism, the condition of patients with severe COVID-19 requiring prolonged mechanical ventilation is often complicated by bacterial ventilator-associated pneumonia [47] and bloodstream infections [48], which might result in an ARDSexp-like pattern overlapping with COVID-19. These mechanisms of viral and inflammatory alveolar and vascular disruption have been referred to as pneumolysis [49,50] and vascular lysis [51,52], respectively.

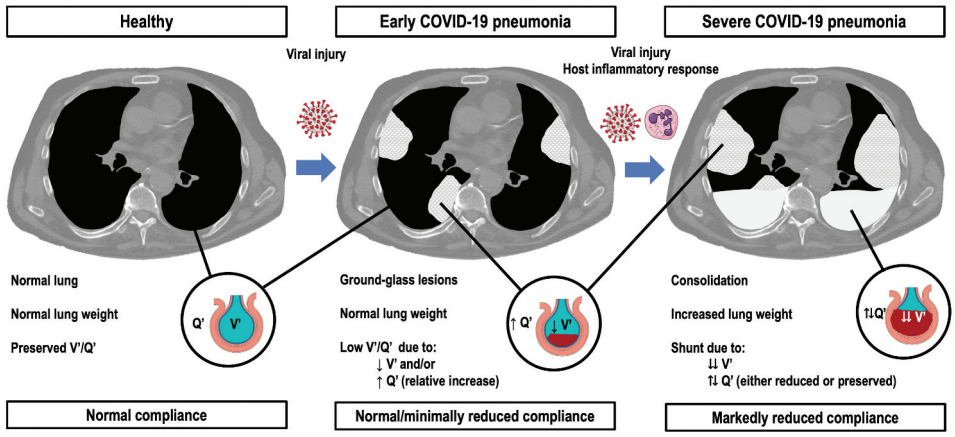

Figure 1. Evolution of lung damage in COVID-19.

4. Distribution of aeration and perfusion in typical ARDS

The pulmonary and extrapulmonary routes of lung injury result in different spatial distribution of lesions in experimental models of ARDSp, where multiple foci of pulmonary injury show heterogeneous spatial distribution, and ARDSexp, where a more diffuse and homogeneous pattern is observed [24]. This is reflected by different radiographic findings reported in clinical studies, with more consolidation observed in ARDSp and more diffuse ground-glass opacification in ARDSexp [24]. Figure 2 summarizes the key pathophysiologic mechanisms in typical ARDS and COVID-19.

4.1. Loss of aeration in typical ARDS

In patients with ARDSexp, alveolar-capillary lesions lead to increased interstitial and alveolar edema (excess tissue mass) homogeneously distributed from ventral to dorsal lung regions. The edema replaces an equal amount of gas space, maintaining the total lung volume constant or slightly reduced (15% decrease in cephalocaudal dimensions of the lung [53] associated with a gravitational increase in density). This might be explained by several factors: the thoracic shape, lung weight, and the gravitational distribution of the blood in the lung capillaries [54]. All these factors contribute to the progressive increase in pleural pressure along the vertical axis,

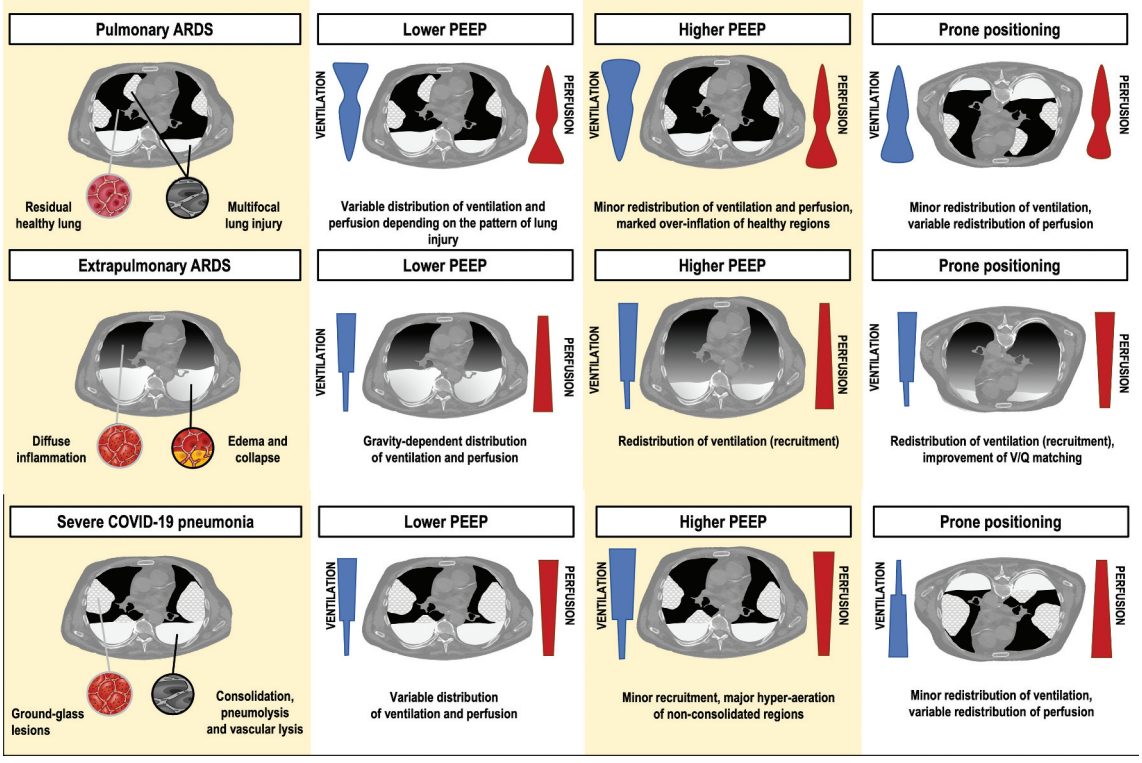

Figure 2. Model describing the response to positive end-expiratory pressure (PEEP) and prone positioning in conventional pulmonary and extrapulmonary acute respiratory distress syndrome (ARDS) and in severe COVID-19 pneumonia.

decreasing the transpulmonary pressure (airway pressure minus pleural pressure), which is the distending force of the lung [55]. The increased pleural pressure (2–3 cmH_2O in normal lungs and 6–8 cmH_2O in ARDS lungs) as well as increased superimposed pressure (5–6 cmH_2O in normal lungs and 10–12 cmH_2O in ARDS lungs) due to the increased lung weight promotes the collapse of alveoli, particularly in most dependent lung regions in the supine position [55]. Whereas the thoracic shape and blood distribution are constant, what changes in ARDS is the superimposed pressure (weight of the lung), which is doubled or tripled compared with normal lungs. Experimental work has shown that the superimposed pressure changes, as measured by computed tomography (CT) imaging, are strictly correlated with pleural pressure changes, measured directly at various lung levels in the pleural space [56,57].

4.2. Distribution of perfusion in typical ARDS

Several techniques for assessment of lung perfusion, including electrical impedance tomography (EIT), depict perfusion but do not consider the different lung densities in the ventral to dorsal gradient [58,59]. On the other hand, positron emission tomography and dual-energy computed tomography (DECT) allow perfusion to be normalized to the perfused lung tissue mass, but these imaging techniques are rarely implemented in clinical practice and in clinical studies. When inhomogeneous lung density is accounted for, perfusion in ARDS has a bell-shaped distribution along the ventral–dorsal axis, and intermediate regions are most perfused, with minimum changes in such shape when different PEEP levels are applied [60]. In addition to perfusion changes due to redistribution of blood flow and aeration, pulmonary coagulopathy has been described in ARDS [61], mediated by activation of the tissue factor pathway [62]. This may result in pulmonary capillary thrombosis, which is reported in 24% of patients with confirmed ARDS and diffuse alveolar damage [63].

4.3. Ventilation–perfusion matching in typical ARDS

Even if the absolute amount of perfusion is nearly normal in non-aerated regions, the ventilation/perfusion (V′/Q′) ratio nears zero due to the massive loss of aeration occurring in the dependent regions. These regions act as a shunt, which is the main determinant of hypoxia in conventional ARDS [64]. Poorly aerated regions might also play a role because they may receive proportionally more perfusion than aeration, thus functionally acting as non-shunt low V′/Q′ areas ($V'/Q' < 1$), but their role is overwhelmed by true shunt regions ($V'/Q' = 0$) in conventional ARDS. Gas exchange in conventional ARDS is the result of the interaction between (1) aerated and perfused lung regions mainly located in non-dependent lung regions; (2) atelectatic lung regions, mainly located in the dependent lung regions; (3) consolidated lung regions prevalently distributed across the vertical gradient [65] or in the dependent part of the lung [66]; (4) minor amount of poorly aerated lung regions, distributed between aerated and collapsed lung regions.

5. Response to PEEP and prone positioning in typical ARDS

This model explaining gas exchange impairment in conventional ARDS has been further corroborated by the fact that progressive increases in pressure at end-inspiration [67] and at end-expiration [65] are associated with better aeration in dependent lung regions and more homogeneous distribution of aeration and ventilation from non-dependent to dependent lung regions. Overall, across different studies, the amount of recruitable tissue related to the excess tissue mass located in the non-aerated regions ranges from 9% to 25% of the total lung weight, suggesting the role of compression atelectasis in determining the amount of recruitable tissue [54,57,66]. In addition, prone positioning, homogenizing the pleural gradient, can redistribute aeration from non-dependent to dependent lung regions, suggesting a relevant role of atelectatic alveoli in determining changes in aeration in ARDSexp [68]. Thus, improvement in oxygenation in prone position is mainly due to alveolar recruitment and increased regional ventilation, with limited changes in the distribution of perfusion [69]. These physiologic gains in prone positioning could reduce ventilator-induced lung injury and improve mortality. Randomized trials showed conflicting results [70,71], but the most recent study, applying prolonged cycles of prone positioning in early, severe ARDS showed a significant reduction in mortality [72].

6. Distribution of aeration and perfusion in severe COVID-19

Two phenotypes of COVID-19 pneumonia have been described [5,6], the first characterized by lower lung weight, higher aeration, and lower amount of non-aerated tissue, and the second characterized by higher lung weight, lower aeration, and higher amount of non-aerated lung tissue (Figure 1). Patients able to maintain noninvasive respiratory support are characterized by better aeration and less poorly aerated and non-aerated tissue; in contrast, patients who require invasive mechanical ventilation are characterized by lower aerated tissue, and higher poorly aerated and non-aerated tissue [48]. The key pathophysiologic mechanisms in severe COVID-19 pneumonia are summarized in Figure 2.

6.1. Loss of aeration in severe COVID-19

Severe COVID-19 pneumonia requiring invasive mechanical ventilation has an ARDS-like pattern of loss of aeration, with large amounts of non-aerated regions [73,74]. In these patients, the lung weight is roughly equivalent to that reported in ARDSexp [29,74], as is reduced respiratory system compliance [12,74]. Nonetheless, several specific aspects of COVID-19-related respiratory failure can be highlighted. Similar to ARDSexp, COVID-19 lungs are characterized by a predominance of non-aerated tissue in dependent regions in the advanced phases of the disease, with poorly aerated ground-glass lung regions homogeneously distributed from non-dependent to dependent lung regions, typically reaching the pleura [75]. Respiratory system compliance tends to be

inversely associated with the severity of hypoxemia in ARDS [76], but these two parameters might be de-coupled in COVID-19, with severe hypoxemia also observed in patients with relatively preserved compliance [74]. In a study comparing severe COVID-19 with ARDS from other causes, hypoxemia was more severe in COVID-19 than in ARDS when matched for similar respiratory system compliance [77]. These factors question the validity of the PaO_2/FiO_2 ratio as a single physiological parameter to define the severity of lung function impairment, which is a cornerstone of the Berlin definition of ARDS. In fact, the decoupling of oxygenation and compliance might result in COVID-19 patients with very low PaO_2/FiO_2 ratio but relatively preserved compliance and normal inspiratory drive, which may not require invasive ventilation.

6.2. Distribution of perfusion in severe COVID-19

Different from ARDSexp, regional perfusion shows a non-gravitational distribution that is higher in non-dependent (more aerated) and less in dependent (non-aerated) lung regions [51]. Patients with COVID-19 have a high incidence of pulmonary capillary microthrombosis [78], pulmonary embolism [79], and venous thrombosis [80], reflected by levels of D-dimers higher than those reported with other causes of pneumonia [81], which are independently associated with increased mortality [82]. Compared with historical cohorts of patients who died from Spanish flu, the incidence of pulmonary macrothrombi in COVID-19 autopsy studies is markedly higher [83]. These findings seem compatible with a COVID-specific de novo coagulopathy with in situ pulmonary clot formation and activation of systemic coagulation pathways [84]. No specific differences in regional antigravitational distribution in perfusion have been detected between patients with early COVID-19 receiving noninvasive respiratory support and those under invasive ventilation [51].

6.3. Ventilation–perfusion matching in severe COVID-19

As much as one-third of the lung volume in severe COVID-19 receives wasted ventilation, i.e. it is characterized by regions with a high V′/Q′ ratio (V′/Q′ > 1) or dead space (V′/Q′ = ∞) [73]. This wasted ventilation distributes primarily in non-dependent lung regions, and non-aerated perfused lung tissue is prevalent in the dependent part of the lung. Interestingly, areas with low V′/Q′ are homogeneously distributed from non-dependent to dependent lung areas [51]. Regions with a low V′/Q′ ratio contribute more to impaired oxygenation in patients receiving noninvasive compared with invasive respiratory support; however, true shunt alone in invasively ventilated patients does not fully explain hypoxemia, as observed in vivo using DECT [51] and in a computational model [85]. One-third of non-aerated tissue is also characterized by non-perfused lung regions [51]. When these perfusion defects are in poorly aerated or non-aerated compartments, this might have a partial protective effect on gas exchange impairment by diversion of blood flow toward non-injured lung regions, minimizing the further deterioration of gas exchange due to low V′/Q′ and true shunt. The hypothesis is that high V′/Q′ areas are characterized by lower perfusion due to microthrombi and/or hyperinflation and that ground-glass and consolidated regions are partly excluded from lung perfusion by local thrombosis.

7. Response to PEEP and prone positioning in severe COVID-19

Several studies have investigated the effects of PEEP in COVID-19, using either CT or EIT. Application of higher levels of PEEP was associated with limited alveolar recruitment in most patients with COVID-19, suggesting that non-aerated tissue is mainly characterized by consolidated, non-atelectatic lung regions [73,86]. Whereas the combination of recruitment maneuvers plus PEEP increased the amount of recruited lung tissue [87,88] compared with increasing PEEP alone [73,86], all studies consistently reported worsening of respiratory system elastance at higher PEEP. This suggests that, in invasively ventilated patients with COVID-19, PEEP levels necessary to achieve clinically meaningful lung recruitment are also associated with relevant overinflation of the non-dependent regions. Prone positioning has been used extensively in both awake [89] and sedated, intubated [90] patients with COVID-19. Although no randomized study has evaluated the efficacy of prone positioning in intubated patients with COVID-19, improvement in oxygenation has been widely reported [90,91]. However, in contrast to what occurs in most patients with ARDSexp, increase in $PaCO_2$ is often observed in COVID-19 after pronation [90,92]. This might suggest that part of the non-perfused dorsal regions may receive more ventilation thus resulting in dead space and worse CO_2 washout. This ventilation could be inefficient and may be solely a distention of the alveoli with poor ventilation, giving rise to increased dead space. However, these pathophysiological hypotheses warrant confirmation in experimental and clinical studies. Moreover, the efficacy of prone positioning in invasively ventilated COVID-19 patients remains to be systematically tested in large, randomized trials.

8. Conclusions

ARDS is a complex syndrome with several causes of pulmonary and extrapulmonary lung injury. COVID-19 represents a specific sub-type of pulmonary ARDS, in which hypoxia is explained by the coexistence of scarcely recruitable non-aerated regions and large areas of low ventilation–perfusion ratio. In the initial phases, patients with COVID-19 could be managed noninvasively and respond to high concentrations of inspired oxygen. However, later stages of the disease typically require invasive ventilation and might show limited improvement with the application of higher PEEP levels. Further research is warranted to better elucidate disease-specific aspects of ARDS from causes other than COVID-19.

9. Expert opinion

Since the earliest definition of ARDS, a unifying approach was widely applied to identify therapeutic strategies, including

personalized ventilatory settings, that might be applied independently of the cause of lung damage and respiratory failure. This attempt to lump altogether different causes of lung diseases in a single entity is convenient and frequently applied in clinical practice. On the other hand, this simplistic view of ARDS might miss several disease-specific aspects of different pathologies. A first attempt to distinguish two entities within the definition of ARDS was performed by classifying it based on pulmonary and extrapulmonary causes of lung injury. This classification provided important insights in the understanding of ARDS, but whereas experimental models had clear differences based on how lung injury was established, the clinical separation between these two entities is often blurred. Lack of clear evidence of different ventilatory strategies acting differently in patients with pulmonary versus extrapulmonary ARDS boosted research toward more sophisticated phenotyping of ARDS. Currently, several phenotypes classification methods for ARDS are under investigation based on clinical and laboratory parameters, with promising results and potential clinical implications relevant to the respiratory management of these patients. The ongoing COVID-19 pandemic has provided the opportunity to study extensively a homogeneous group of patients fulfilling the clinical criteria for ARDS but sharing the same underlying cause of lung damage. COVID-19 pneumonia is a cause of pulmonary ARDS. Compared with other causes of pulmonary ARDS, patients with COVID-19 show early endothelial activation and dysfunction. This translates into a high incidence of pulmonary and systemic hypercoagulability, which affects the distribution of pulmonary blood and regional perfusion. Patients with COVID-19 have a heterogeneous distribution of different ventilation–perfusion patterns, with predominance of low V′/Q′ in the early stages overlapping with a true shunt in the most advanced, severe cases.

In severe COVID-19, elastic properties of the lungs are not always coupled to the severity of hypoxemia, as it occurs in typical ARDS. This brings into question the use of the PaO_2/FiO_2 ratio as a single indicator of the severity of the disease; this is a commonly applied strategy in typical ARDS, where cutoffs of the PaO_2/FiO_2 ratio are part of guidelines and recommendations on the indication for intensive care admission, initiation of noninvasive positive pressure respiratory support, invasive mechanical ventilation, and rescue strategies, including prone positioning and extracorporeal membrane oxygenation. The spatial distribution of loss of aeration is similar in ARDS and severe COVID-19, but the response to higher PEEP levels is modest and often accompanied by worsening of respiratory system compliance. Also, a paradoxical increase in $PaCO_2$ is often seen during prone positioning in COVID-19, suggesting diversion of ventilation toward scarcely perfused dorsal regions. During the ongoing COVID-19 pandemic, unprecedented use of noninvasive respiratory support has been reported, even in patients with gas exchange impairment previously considered as a strict indication for intubation. However, cautious monitoring of patients receiving noninvasive respiratory support is mandatory in COVID-19, since patients ultimately requiring intubation must be identified timely to avoid further progression of disease. It is yet to be determined how this renewed interest in noninvasive management of respiratory failure will change our research agenda and our clinical practice in non-COVID-19 ARDS. Further research is warranted to better elucidate disease-specific aspects of ARDS from causes other than COVID-19.

Declaration of interest

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