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REVIEW

Physiology in Medicine

Functional pathophysiology of SARS-CoV-2-induced acute lung injury and clinical implications

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Abstract

The worldwide pandemic caused by the SARS-CoV-2 virus has resulted in over 84,407,000 cases, with over 1,800,000 deaths when this paper was submitted, with comorbidities such as gender, race, age, body mass, diabetes, and hypertension greatly exacerbating mortality. This review will analyze the rapidly increasing knowledge of COVID-19-induced lung pathophysiology. Although controversial, the acute respiratory distress syndrome (ARDS) associated with COVID-19 (CARDS) seems to present as two distinct phenotypes: type L and type H. The "L" refers to *low* elastance, ventilation/perfusion ratio, lung weight, and recruitability, and the "H" refers to *high* pulmonary elastance, shunt, edema, and recruitability. However, the LUNG-SAFE (Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure) and ESICM (European Society of Intensive Care Medicine) Trials Groups have shown that ~13% of the mechanically ventilated non-COVID-19 ARDS patients have the type-L phenotype. Other studies have shown that CARDS and ARDS respiratory mechanics overlap and that standard ventilation strategies apply to these patients. The mechanisms causing alterations in pulmonary perfusion could be caused by some combination of *1*) renin-angiotensin system dysregulation, *2*) thrombosis caused by loss of endothelial barrier, *3*) endothelial dysfunction causing loss of hypoxic pulmonary vasoconstriction perfusion control, and *4*) hyperperfusion of collapsed lung tissue that has been directly measured and supported by a computational model. A flowchart has been constructed highlighting the need for personalized and adaptive ventilation strategies, such as the time-controlled adaptive ventilation method, to set and adjust the airway pressure release ventilation mode, which recently was shown to be effective at improving oxygenation and reducing inspiratory fraction of oxygen, vasopressors, and sedation in patients with COVID-19.

ARDS; COVID-19; SARS-CoV-2; TCAV

OVERVIEW OF SARS-CoV-2 LUNG PATHOPHYSIOLOGY

Introduction

Infection caused by the novel coronavirus SARS-CoV-2 rapidly progressed into a global pandemic, with more than 84.4 million reported cases worldwide at the time of this review's submission (1). Although age and comorbidity dependent, age stratification suggests that those below 74 yr of age have a 99% survival rate, with the greatest mortality above 74 yr of age at 95%, indicating that the majority of patients testing positive for SARS-CoV-2 recover or remain asymptomatic (2). However, certain at-risk populations and select comorbidities are associated with more severe manifestations of the virus (3–5). Progression to acute respiratory distress syndrome (ARDS) has been reported in up to 20% of SARS-CoV-2 pneumonia cases, with nearly 41% in patients who are hospitalized (6). Early on, however, some patients requiring intubation have substantially preserved lung compliance, indicating pulmonary pathology differing from what is typically seen in ARDS. Furthermore, alterations in lung perfusion regulation in patients with SARS-CoV-2 have been suggested as contributing to hypoxemia necessitating mechanical ventilation (MV) (7, 8) as well as direct vascular injury leading to hypercoagulability, pulmonary microthrombi, and pulmonary embolism (9–15).

Although the median arterial partial pressure of oxygen/inspiratory fraction of oxygen ($Pa_{O_2}/F_{I_{O_2}}$) ratio at presentation with SARS-CoV-2 can be categorized as moderate-to-severe ARDS (~150, ranging from 103 to 182 ratio) (16, 17), many patients do not exhibit radiological involvement of dependent lung collapse associated with alteration of lung mechanics (Fig. 1*A*) commonly seen in ARDS caused by other mechanisms and in Type-H CARDS (Fig. 1*B*) (18). Indeed, severe hypoxemia and large shunt fractions can coexist with relatively

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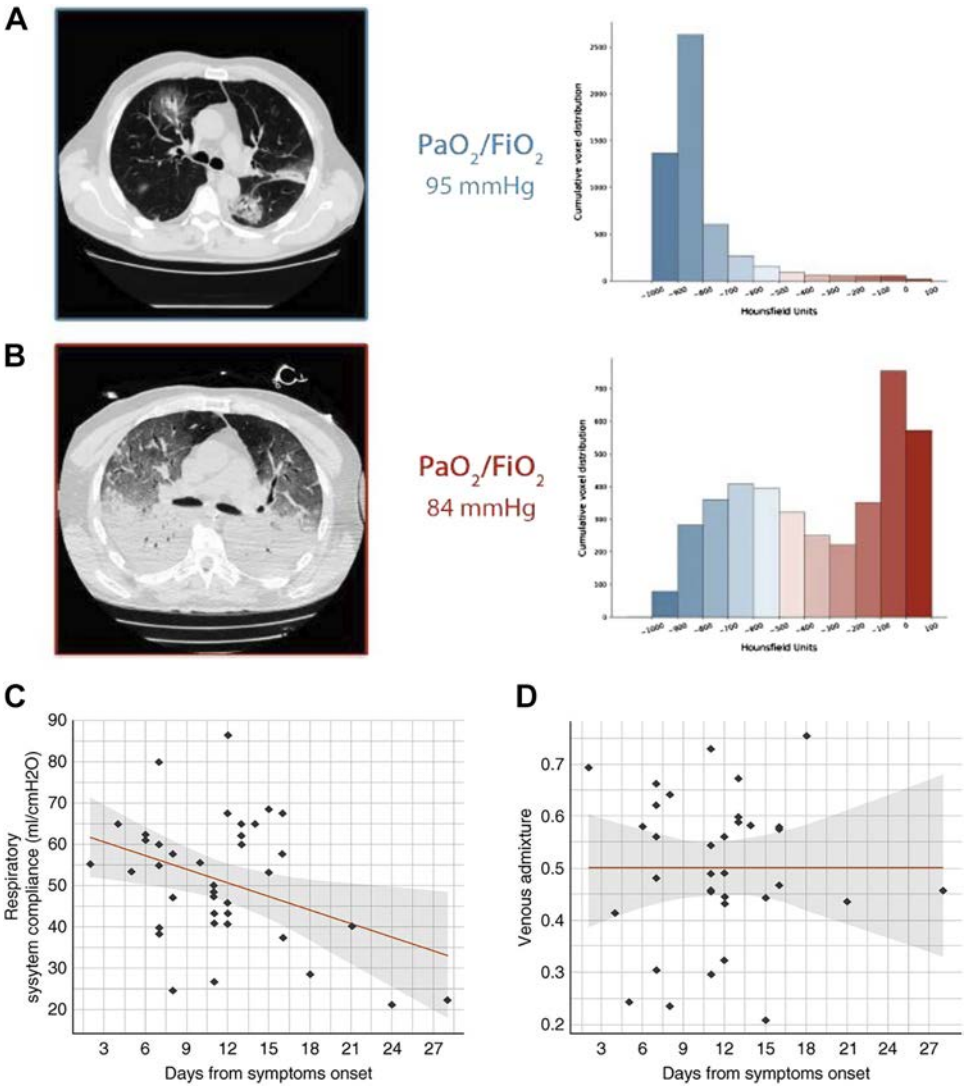

Figure 1. *A*: CT scan from patients with SARS-CoV-2 during spontaneous breathing. Blue bars are color coded for less dense, and red bars are color coded for denser. The entire lung is well aerated (large percentage of blue bars), with most of the Hounsfield units (HU) ranging between −800 and −1,000 (an HU of −1,000 = density of air) with almost no nonaerated tissue (red bars 0HU = density of pure water). FI_{O_2} on a venturi mask was 80% with a Pa_{O_2}/FI_{O_2} ratio of 95 mmHg. *B*: CT scan taken on mechanical ventilation at end-expiration with a PEEP of 5 cmH_2O. The CT scan is shifted to the right (nonaerated compartment), while the aerated compartments are greatly reduced. FI_{O_2} was 70% with a Pa_{O_2}/FI_{O_2} ratio of 84 mmHg. *C*: in a series of 28 patients, there was a strong correlation of a fall in respiratory system compliance with an increase in number of days from symptom onset. *D*: no correlation between the number of days from symptom onset and venous admixture (7, 18). Reproduced from Refs. (7) and (18) under Creative Commons License 4.0. FI_{O_2}, inspiratory fraction of oxygen; Pa_{O_2}, arterial partial pressure of oxygen.

normal lung volumes and a near-normal lung compliance. The dissociation between changes in lung mechanics and severity of hypoxemia has advanced the hypothesis that SARS-CoV-2 produces an atypical form of ARDS (Fig. 1) (8).

SARS-CoV-2 seems to affect the regulation of pulmonary perfusion, and earlier in the course of the disease may have functional (e.g., loss of hypoxic vasoconstriction, vasoplegia, inflammatory hyperemia) or anatomical alterations in pulmonary perfusion, which may affect patients with more susceptible vascular endotypes (Fig. 2) (20–23). The average ratio between shunt fraction and the fraction of gasless tissue found on quantitative computerized tomography (CT) was more than double compared with the ratio found in more typical ARDS, suggesting a significant hyperperfusion of gasless tissue (Figs. 1 and 2) (24, 25).

Studies have described vessel enlargement in the vicinity of ground-glass opacities, with subsegmental vascular enlargement (>3 mm in diameter) observed in 90% of patients diagnosed with SARS-CoV-2 (31). Dual-energy CT scans provide evidence of pulmonary shunting and increased perfusion (26–28). Pulmonary vessel enlargement has also been shown in areas where new lung infiltrates develop in the follow-up CT scan (29) with decreased perfusion and peripheral ischemic lung areas not associated with macrothromboses (Fig. 2, *C* and *D*) (27, 28, 30). These alterations increase perfusion around areas of consolidation and injured lung and hypoperfusion in normal parenchyma (31). These perfusion abnormalities may explain the gas exchange and lung mechanics dissociation seen in SARS-CoV-2 and the response to supportive treatment (32). Although it appears that hypoperfusion of the small amount of collapsed or edema-filled tissue is what causes the high pulmonary shunt seen in patients with COVID-19, the mechanisms for these phenomena are not fully understood.

Possible Mechanisms of Altered Pulmonary Perfusion

Postmortem findings confirm both clinical and radiological evidence of angiogenesis in an early stage of diffuse alveolar damage and distinctive vascular features of severe endothelial injury and angiogenesis predominantly through a mechanism of intussusceptive angiogenesis nearly three times higher than seen in a matched cohort of patients with

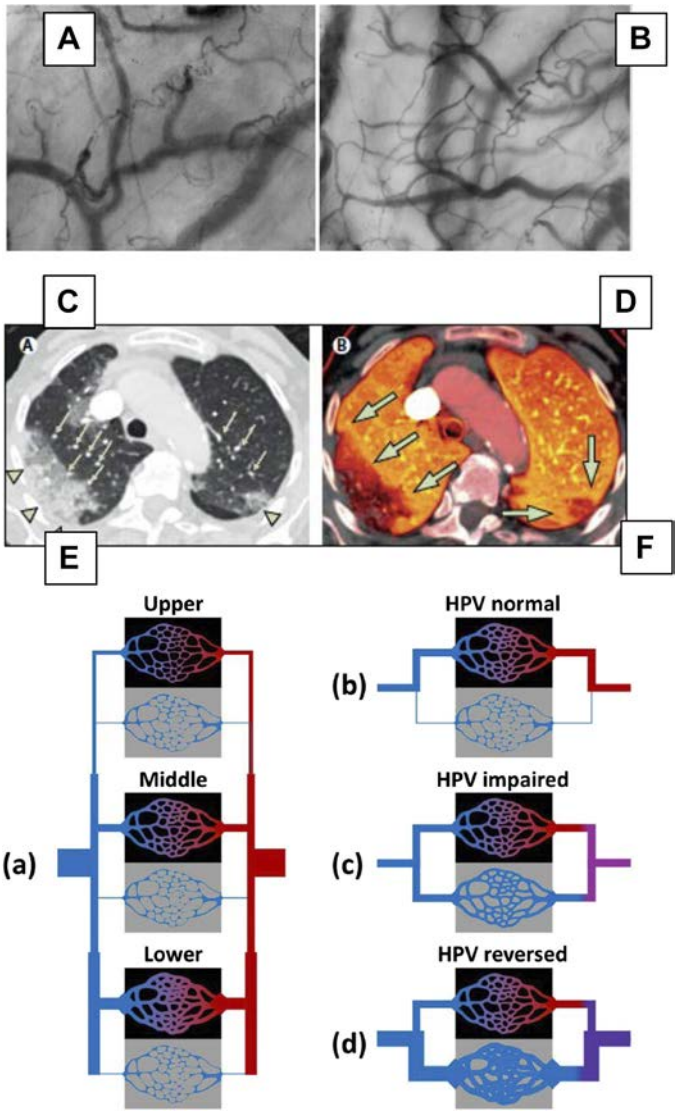

Figure 2. COVID-19 impact on systemic and pulmonary perfusion. *A*: reduced systemic microvessel density (sublingual) in a patient with a high circulating level of the fibrin degradation product known as D-dimer (6367 ng/mL Pa_{O_2}/FI_{O_2} = 74). *B*: sublingual perfusion density was markedly increased in a patient with a lower D-dimer level (741 ng/dL, Pa_{O_2}/FI_{O_2} = 247) (76). *C*: dual-energy CT showing a large dependent area of lung collapse (arrow heads), which is accompanied by dilated pulmonary vessels near and within areas of lung collapse (arrows) in a patient with SARS-CoV-2. *D*: in the same patient, there was a large increase in blood flow (hyperperfusion) into and around the areas of collapsed lung [arrows, dark orange (28)]. *E*: computational model of aerated lung (black box) and nonaerated lung (grey box) at the top, middle, and bottom of the lung (*a*). The amount of perfusion is depicted by the diameter of the capillary bed. *F*: the perfusion pattern with normal HPV (*b*), impaired HPV (*c*), and reversed HPV (*d*). With normal HPV, the perfusion is greater in the aerated than the nonaerated lung tissue; with impaired HPV, the perfusion is equal; and with reversed HPV, the perfusion is highest in the nonaerated tissue (80). Figure 2, *A, B, E,* and *F*, reproduced from Refs. (76) and (80) under Creative Commons License 4.0. Figure 2, C and D, reproduced with permission from Ref. (28) under license 4945480646537. FI_{O_2} inspiratory fraction of oxygen; Pa_{O_2}, arterial partial pressure of oxygen.

influenza (20), with the degree of angiogenesis concomitant with increasing duration of hospitalization (20). Histopathology from a patient with SARS-CoV-2 pneumonia demonstrates severe acute lung injury (ALI) (Fig. 3, *A–D*) with an organizing pneumonia pattern of fibrosis, congested alveolar capillaries, endothelial involvement, collapsed alveolar walls, and atelectasis. The endothelial and epithelial cells had normal angiotensin-converting enzyme 2 (ACE2) receptor expression (Fig. 3*D*). Capillaries remain well perfused in areas of alveolar wall collapse and atelectasis, suggesting loss of hypoxic pulmonary vasoconstriction (HPV) and matching of ventilation (V) with perfusion (Q) (i.e., V/Q ratio) (Fig. 3*C*).

Additional radiological and pathological studies report increased rates of micro- and macrovascular thrombosis (20, 24), with alveolar capillary microthrombi nine times as prevalent in patients with SARS-CoV-2 versus those with influenza (20). Any combination of mechanisms that alter lung ventilation and perfusion ratio (V/Q) including vasodilation and angiogenesis, hypoperfusion of open lung, hyperperfusion of collapsed lung tissue, vasoconstriction, and thrombogenesis (immunothrombosis) can explain the increase in shunt and dead space seen in patients with COVID (33–35). Although ARDS from all causes alters the V/Q ratio, the difference with CARDS is that the extent of consolidative changes is disproportionate to gasless tissue and lung mechanics. In an initial report, Lang et al. (28) using dual-energy CT (DECT) shed more light on the possible mechanisms for the loss of V/Q control. They found a preferential increase in perfusion surrounding consolidation, decreased peripheral perfusion, and vascular dilation. In a subsequent study also using DECT, they showed that 15% of the 48 patients studied had pulmonary emboli, whereas a much larger percentage of the patients (85%) had dilated vessels extending to the pleural surface that were present both within and outside of lung opacities. Regional hyperemia within or surrounding opacities was seen in 52% of the patients, with corresponding oligemia in 96% of the patients (27). Afat et al. (26) in 14 patients with COVID-19 without macroscopic emboli also found pulmonary perfusion defects but in a smaller proportion as compared with the glass opacities identifying consolidation. They concluded that the most logical explanation for the perfusion defect was microperfusion pathologies. High-altitude pulmonary edema (HAPE) also causes pulmonary perfusion defects and thus may offer clues to COVID-19-induced alterations in pulmonary blood flow. Unfortunately, the pulmonary vascular pathophysiology caused by COVID-19 differs from that caused by HAPE in that it is likely mediated by vasodilation secondary to inflammation, whereas HAPE is caused by uneven pulmonary vasoconstriction (36). Combined these studies suggest that COVID-19 causes pulmonary perfusion dysregulation associated with vascular derangement, but, as of yet, there is no clear-cut mechanism. However, detailed evidence of spatial and time determinants, topographical issues, and disease progression of these pulmonary perfusion defects is not yet available.

Evolution of the disease and supportive management such as mechanical ventilation and shock resuscitation leads to increasing lung edema and consolidation, producing less recruitability and a reduction in lung volume (37), reflected by the decrease in lung compliance leading to a clinical phenotype more similar to ARDS caused by other mechanisms (i.e., bacterial sepsis or pneumonia, hemorrhagic shock, massive trauma, and burns) and ultimately lung fibrosis,

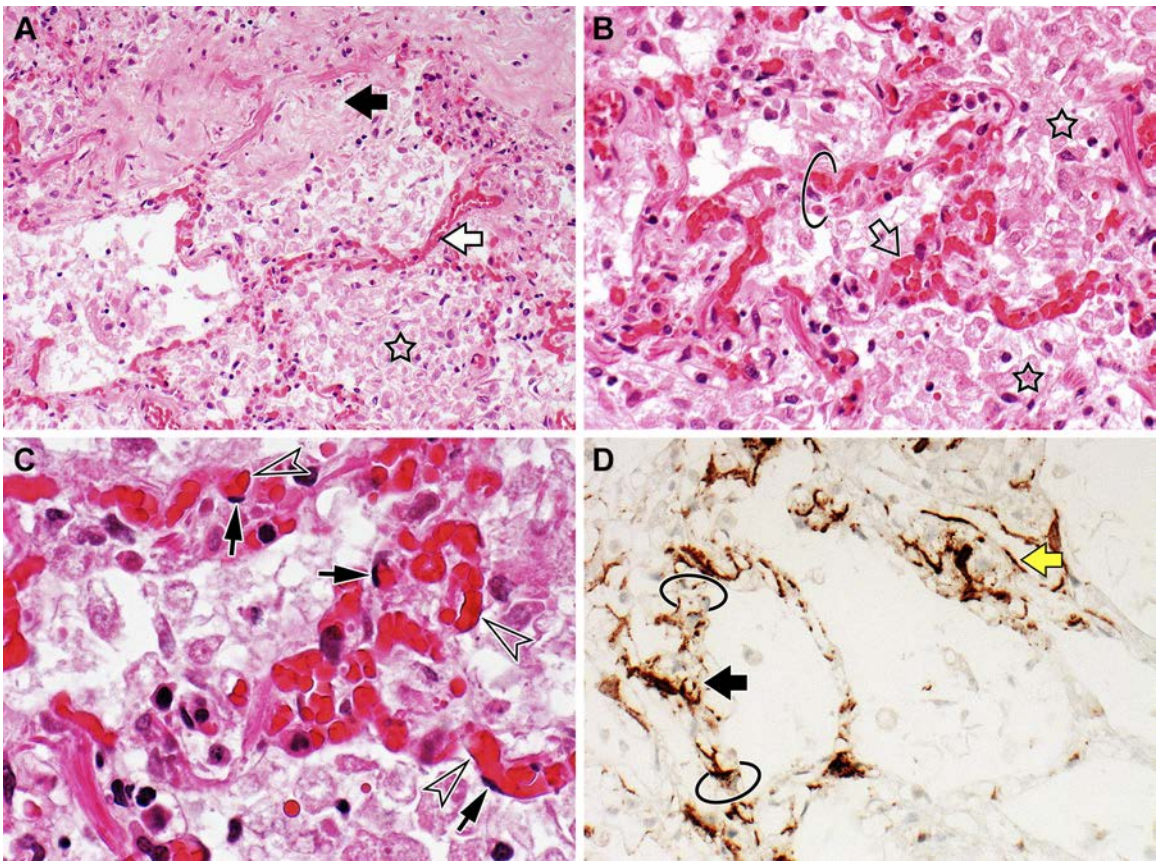

Figure 3. Our analysis of postmortem lung tissue from patients with COVID-19. *A*: postmortem SARS-CoV-2 lung at low magnification. Organizing pneumonia pattern of fibrosis (*black arrow*). Congested alveolar capillaries (*white arrow*) in area of atelectasis (*star*) (hematoxylin and eosin ×100). *B*: postmortem SARS-CoV-2 lung at medium magnification. Collapsed alveolar walls (*circled*) in area of atelectasis (*star*). Alveolar capillaries show marked congestion (*arrow*) and are packed with red blood cells (hematoxylin and eosin ×200). *C*: postmortem SARS-CoV-2 lung at high magnification. Detailed view of alveolar capillaries showing endothelial cell nuclei (*arrows*) and the presence of cytoplasmic accretions (*arrowheads*) indicative of endothelial involvement (hematoxylin and eosin ×400). *D*: postmortem SARS-CoV-2 lung immunohistochemistry showing alveolar walls (*circled*) with ACE2 receptor expression in alveolar epithelial cells (*black arrow*) and endothelial cells (*yellow arrow*) (immunoperoxidase ×200).

organizing pneumonia, and fibrin deposits (Figs. 1*B* and 2, *C* and *D*) (20, 24, 38, 39). These temporal changes have implications for treatment and ventilatory strategies for patients with SARS-CoV-2 pneumonia (40–42). Understanding the functional lung pathophysiology of COVID-19 is necessary to determine the treatment of SARS-CoV-2-induced acute lung injury in the clinic (Fig. 4). The following section will detail our current understanding of functional lung pathophysiology and how to use this understanding to better treat the patient with COVID-19.

ALTERATION OF PULMONARY PERFUSION: A RAMIFICATION OF SEVERE ENDOTHELIAL CELL INJURY

Introduction

A striking difference between SARS-CoV-2 and bacterial sepsis-induced ALI is alterations in blood flow to normally aerated lung tissue. Bacterial sepsis-induced ARDS, as well as ARDS caused by trauma, hemorrhagic shock, or burns, causes an increase in pulmonary capillary permeability and results in a high-permeability edema that produces alveolar flooding and collapse, primarily altering oxygenation and ventilation secondary to loss of alveolar surface area, rather than abnormalities of perfusion (43). Increasing perfusion to capillaries with increased permeability would exacerbate the rate of edema accumulation (44).

Possible explanations for this pathological perfusion anomaly include disruption of the renin-angiotensin system (RAS) and severe damage to the vascular endothelium inhibiting HPV and macro- and microembolization (Fig. 4). SARS-CoV-2 initiates a systemic inflammatory response syndrome (SIRS) with a massive release of inflammatory mediators causing a "cytokine storm" (45–47), which can cause pulmonary endothelialitis, thrombosis, and vasodilation that may contribute to the hyperperfusion of collapsed lung tissue (20, 27, 31).

Hypoxia without Lung Collapse

Although controversial (48), it has been suggested that there are two distinct subphenotypes of SARS-CoV-2-induced ALI. Gattinoni et al. (49) have referred to these phenotypes as SARS-CoV-2 pneumonia type "L" and type "H".

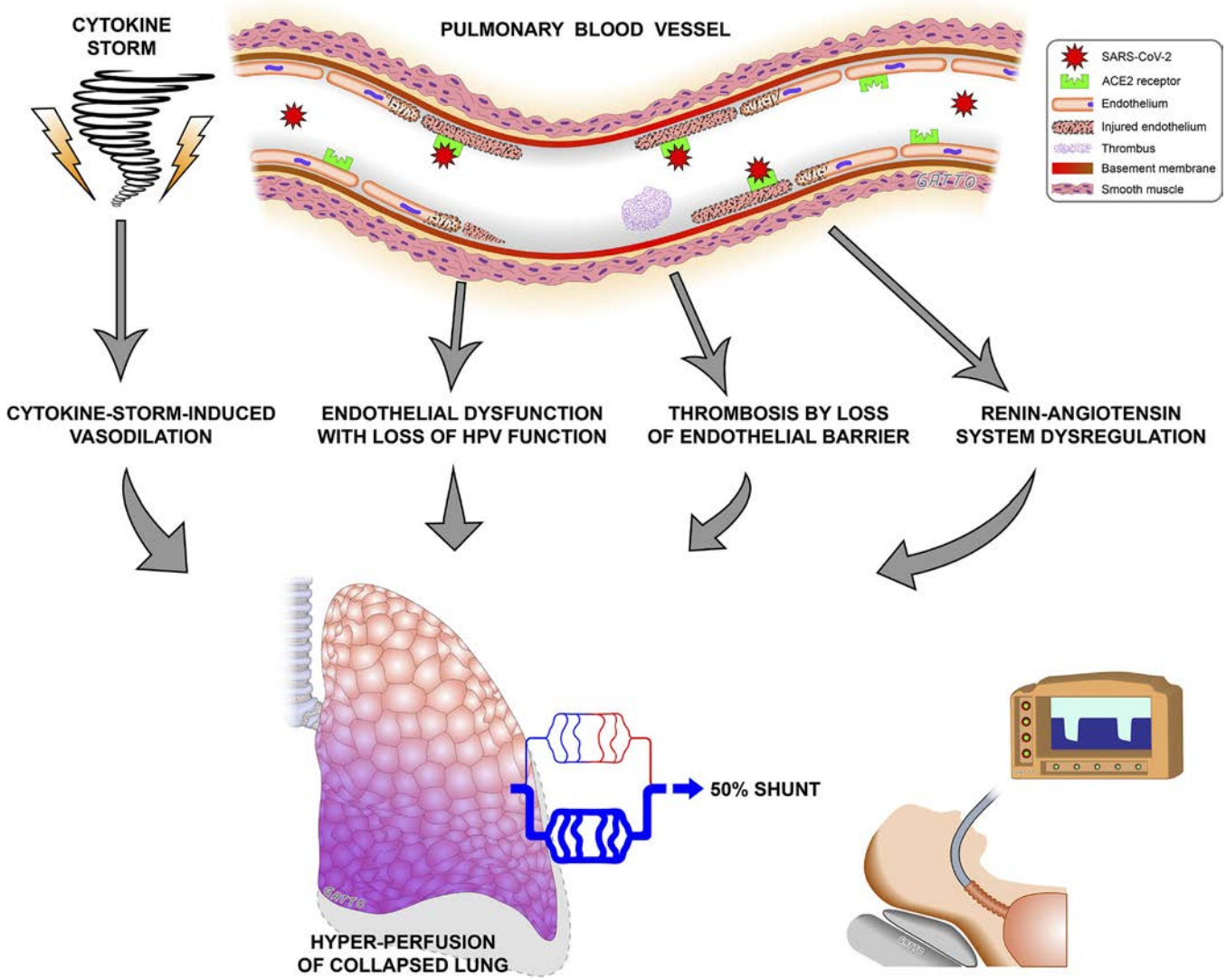

Figure 4. Possible mechanisms causing the loss of perfusion control and V/Q mismatching in patients with SARS-CoV-2-induced pneumonia. *Renin-angiotensin system (RAS) dysregulation*: SARS-CoV-2 enters the endothelial cell through the angiotensin-converting enzyme 2 (ACE-2) receptor (52) on the cell surface causing endotheliali tis (20, 60). Downregulation of the ACE-2 receptor prevents angiotensin II from being converted to angiotensin 1–7, which can cause pulmonary vasoconstriction, pulmonary edema, and impaired lung function (61). *Thrombosis by loss of endothelial barrier*: The main mechanism for SARS-CoV-2-induced coagulopathy is believed to be endotheliali tis with damage and death of endothelial cells resulting in a loss of barrier integrity, exposing the thrombogenic basement membrane, which in turn activates the clotting cascade (20, 70). *Endothelial dysfunction with loss of HPV function*: Pulmonary artery endothelial cells (PAECs) and pulmonary artery smooth muscle cells (PASMCs) work in conjunction to regulate HPV (73). SARS-CoV-2 infects endothelial cells, causing an endotheliali tis (20, 74), which may inhibit the ability of the pulmonary smooth muscle to constrict and thus plays a role in loss of V/Q homeostasis. *Cytokine storm-induced vasodilation*: The systemic inflammatory response syndrome (SIRS) causes a "cytokine storm" that results in vascular inflammation, which can cause vasodilation and thus may contribute to the hyperperfusion of collapsed lung tissue (20). *Hyperperfusion of collapsed lung*: Some combination of all the above results in a hyperperfusion of collapsed lung tissue (8, 28, 49, 81, 82) that has been supported by computational modeling (Fig. 2, *E* and *F*) (80).

The "L" refers to *low* elastance, V/Q ratio, lung weight, and recruitability, and the "H" refers to *high* elastance, right to left shunt, lung weight, and recruitability (Fig. 1, *A–D*). A patient with SARS-CoV-2 type L spontaneously breathing on a venturi mask with FI_{O_2} of 80% presented with an open lung with a very low Pa_{O_2}/FI_{O_2} ratio of 95 (Fig. 1*A*). The L-type lung is not only open but also remains relatively compliant. In a group of 16 patients, the respiratory system compliance was 50.2 ± 14.3 mL/cmH_2O, while the shunt fraction was 50.2 ± 0.11% (8). A patient with SARS-CoV-2 H-type pneumonia on volume-controlled mechanical ventilation had severe dependent lung collapse, similar to "typical" ARDS pathology, and a Pa_{O_2}/FI_{O_2} ratio of 84 (Fig. 1*B*). These findings were confirmed in a series of 28 patients showing a strong correlation between the fall in respiratory system compliance (C_{RS}) and the number of days from symptom onset but no correlation between the number of days from symptom onset and the venous admixture (Fig. 1, *C* and *D*) (8). However, the LUNG-SAFE and ESICM Trials Group found a wide range of respiratory system compliance (C_{RS}) in

1,117 mechanically ventilated patients with non-COVID-19 ARDS, with one in eight of these patients having type-L ARDS (C_{RS} > 50 mL/cmH_2O), which challenges the concept that CARDS pathophysiology has two distinct phenotypes (50). They also found that the patients with higher lung compliance had fewer comorbidities and a lower mortality. This relationship between mortality and compliance is less clear in CARDS where markers of immunothrombosis (i.e., D-dimer) had a stronger relationship with outcome (51). Finally, Grasso et al. (52) demonstrated in eight patients with early severe CARDS and C_{RS} ≥50 mL/cmH_2O (type L) that higher PEEP improved oxygenation and aeration but negatively impacted hemodynamics and caused alveolar hyperinflation.

Other studies suggest that there is a large overlap in the respiratory mechanics and pathophysiology of ARDS caused by sepsis or trauma and COVID-19-induced ARDS (51, 53, 54). In a multicenter, prospective, observational study in 742 CARDS patients with ARDS defined by the Berlin criteria, it was shown that lung pathophysiology as determined by C_{RS}, plateau pressure (Pplat), and driving pressure (ΔP) was similar to that of ARDS caused by other etiologies, with >80% of patients with CARDS presenting with a low lung compliance. Mortality was also similar to that in ARDS observational studies (53).

A second study was conducted at Massachusetts General Hospital and Beth Israel Deaconess Medical Center on 66 mechanically ventilated patients with CARDS with a goal to characterize COVID-19-induced respiratory failure (55). They found that $Pa_{O_2}/F_{I_{O_2}}$ ratio, dead space fraction, and lung compliance were similar to those measured in large cohorts of patients with ARDS and that the patients with CARDS responded to prone positioning similar to that measured in patients with ARDS from other etiologies. They suggested that established ARDS therapies including low tidal volume (LVt) and early proning should be used on patients with CARDS. However, Chiumello et al. (56) found that patients with CARDS had a greater lung compliance and significantly greater lung gas volume than patients with ARDS matched for anthropometric characteristics and Pa_{O_2}/FI_{O_2} ratio. In addition, the venous admixture was significantly related to the nonaerated tissue in $Pa_{O_2}/F_{I_{O_2}}$-matched ARDS and compliance-matched ARDS but unrelated in COVID-19-ARDS, suggesting that hypoxemia in CARDS is not only due to the extent of nonaerated tissue.

Although COVID-19-induced ARDS pathophysiology may indeed be atypical (8), this hypothesis has not been subjected to rigorous experimental investigation (48). Growing clinical evidence shows how the phenotype associated with COVID-19 ARDS is crucially dependent on the time from disease to hospitalization and mechanical ventilation. The longer the time from symptoms to measurement of lung mechanics and radiology, the more similar to typical ARDS. This heterogeneity of presentation and case mix may explain why some authors report case series that overlap other ARDS studies, whereas others show that despite similar oxygenation defect, COVID-19 has heterogeneity on lung mechanics with, on average, higher compliance than typical ARDS (57). On this basis, some authors maintain that all patients with COVID-19 should be treated following ARDS guidelines (41, 58), whereas others advocate a treatment based on lung mechanics rather than ventilation management based on the degree of oxygenation defect alone (8).

Severe Endothelial Cell Injury—Dysregulation of the RAS System

SARS-CoV-2 is known to enter the cell through the angiotensin-converting enzyme 2 (ACE2) receptor on the cell surface (Fig. 4) (59). Pulmonary vascular endothelium is rich in ACE2 receptors (Fig. 3*D*), and SARS-CoV-2 virus has been observed in these cells using transmission electron microscopy. The result of this infection is a severe pulmonary vascular endothelialitis (20, 60). The ACE2 system plays a critical protective role in heart and lung disease, and SARS-CoV-2 is known to cause loss of ACE2 function and downregulation by attaching to the receptor (61). ACE2 is a negative regulator of the RAS system by converting angiotensin II to angiotensin 1–7; binds to Mas receptor (Mas-R) to produce anti-inflammatory, antiedema, and antifibrotic actions; and stimulates the release of nitric oxide causing vasodilation (61). The lung is the leading site of angiotensin II synthesis, which is an effective pulmonary vasoconstrictor that can cause pulmonary edema, impair lung function, and modulate hypoxic pulmonary vasoconstriction (HPV) (62–65). In addition, it has been shown that inhibition of ACE2 attenuates HPV (66). Thus, dysregulation of the RAS system is one possible component for the loss of V/Q matching in patients with SARS-CoV-2 (Fig. 4). A physiological review of SARS-CoV-2-induced dysregulation of the RAS system suggests that usage of drugs to normalize RAS might be a way to counter SARS-CoV-2 (67).

Severe Endothelial Cell Injury—Pulmonary Thrombosis

An established pathology of SARS-CoV-2 is activation of coagulation pathways with potential development of disseminated intravascular coagulation (DIC) (68–70). Unlike sepsis-induced coagulation (SIC)/DIC where suppression of fibrinolysis (i.e., the fibrinolytic shutdown) prevents a large increase in the D-dimer, in SARS-CoV-2, D-dimer levels can be five times above the normal range (69). Consumptive coagulopathy typical of SIC/DIC is usually not seen with SARS-CoV-2, with fibrinolysis upregulation in alveoli by urokinase-type plasminogen activator (u-PA) as the mechanism of D-dimer elevation (69).

The main coagulation mechanism is believed to be endothelialitis with damage and death of endothelial cells, resulting in a loss of barrier integrity that exposes the thrombogenic basement membrane and in turn activates the clotting cascade (Fig. 4) (20, 70). Autopsy on patients with SARS-CoV-2 showed in four of seven lungs that thrombi partially blocked the vascular lumen of pulmonary arteries (1–2 mm diameter). In all patients, fibrin thrombi were found in alveolar capillaries and were nine times more prevalent in SARS-CoV-2 as compared with influenza. Thrombi were also found in postcapillary venules but in smaller numbers. Three-dimensional micro-CT showed nearly total occlusion of pre- and postcapillary vessels (20). Recent reviews discussed thrombosis pathophysiology of treating the coagulopathy seen in patients with SARS-CoV-2 (71, 72).

Severe Endothelial Cell Injury—Loss of Hypoxic Pulmonary Vasoconstriction Function

Pulmonary artery endothelial cells (PAECs) and pulmonary artery smooth muscle cells (PASMCs) work in conjunction to regulate HPV (73). SARS-CoV-2 infects endothelial cells, causing an endotheliali tis (20, 74), which may inhibit the ability of the pulmonary smooth muscle to constrict and thus play a role in loss of V/Q homeostasis. The PAECs are a major source of nitric oxide (NO), where endotheliali tis may further alter pulmonary perfusion by reducing the NO concentration. Additional loss of PAECs may occur since they have been shown to be very fragile in a hypoxic environment (73, 75). At this time, we are not sure if loss of pulmonary endothelial cells reduces HPV efficiency, playing a role in the V/Q mismatch seen in SARS-CoV-2 L-type pneumonia (Fig. 1*A*). However, it is clear that some combination of the abovementioned potential mechanisms dramatically affects the homeostasis of ventilation and perfusion (Fig. 4).

SARS-CoV-2-Induced Alteration of Pulmonary Perfusion

A review of possible mechanisms that may be responsible for the unique loss of pulmonary perfusion control caused by SARS-CoV-2 is seen in Fig. 4. Mangalmurti et al. (22) have suggested that SARS-CoV-2-induced ARDS has a distinct vascular endotype , which has been directly shown to alter circulation (28, 76). Damiani et al. (76) used a handheld video-microscope and measured sublingual microcirculation in real time in 29 patients with SARS-CoV-2. They showed that plasma D-dimer concentration was inversely correlated with the density of perfused microvessels ($\leq$20 μm diameter) and hypothesized that the mechanism for the decrease in perfusion was microthrombi (Fig. 2, *A* and *B*). In patients with SARS-CoV-2, Lang et al. (28), using dual-energy CT, showed striking perfusion abnormalities with hyperperfusion of the collapsed lung areas (Fig. 2, *C* and *D*). Notably, HPV not only failed to divert blood from these collapsed lung areas but, rather, perfusion actually increased, which is highly abnormal. The patient's lung showed significant dependent densities and a large increase in blood flow to these nonaerated portions of the lung (Fig. 2, *C* and *D*). Although the D-dimer was high (>1,000 ng/mL), no pulmonary emboli were observed. They did observe a significant proximal and distal vasodilation around, and within, the collapsed lung areas. In a subsequent study of 48 patients with COVID-19, they showed that 15% of the patients had pulmonary emboli, whereas 85% had dilated vessels that were present outside and within lung opacities (27).

Pulmonary vasodilation in patients with COVID-19 pneumonia was also measured using contrast-enhanced transcranial doppler (TCD) (32). There are multiple mechanism(s) by which SARS-CoV-2 could cause HPV failure, including endothelial damage, vasodilation caused by the cytokine storm, pulmonary thrombosis, and dysregulation of the renin-angiotensin system. The authors speculated that HPV may have failed due to a dysfunctional inflammatory process causing the vasodilation. Obviously, increasing blood flow to collapsed lung areas will greatly increase the shunt fraction and is exactly what has been seen in patients with SARS-CoV-2 (8), supporting the initial work by Lang et al. (28). These findings have been confirmed and expanded upon in a recent publication by this group and others (26, 27). Other possible mechanisms that may act additively or synergistically with those mentioned above are mechanical ventilation that can redistribute blood flow into unventilated or collapsed lung regions during inspiration that will cause a decrease in oxygenation (25), and unstable alveoli have been shown to stent open pulmonary vessels, preventing HPV-induced vasoconstriction and increasing continuous capillary perfusion in poorly ventilated areas of alveolar instability and collapse (77, 78). These findings have been seen in other conditions, including portopulmonary hypertension, pulmonary venous hypertension, pulmonary veno-occlusive disease, pulmonary hypertension, and hepatopulmonary syndrome (79). However, in the patients with COVID-19, these changes in pulmonary perfusion were seen using DECT scans without any of the abovementioned comorbidities, suggesting an independent and novel mechanism (26–28).

Herrmann et al. (80) developed a mathematical model for pulmonary perfusion based on the severe hypoxia in patients with SARS-CoV-2 with a mostly open lung (8, 28, 49, 81, 82), which is often "silent" in that the patient does not have the feeling of dyspnea (83). To test the hypothesis that hypoxia in a mostly open lung can be caused by a loss of HPV function, they used their computational model of lung aeration and perfusion (V/Q) and the resultant pulmonary shunt fraction when the V/Q ratio is altered (Fig. 2, *E* and *F*). Their results in an in silico patient with only moderate lung collapse demonstrated that HPV inhibition alone could not account for the extremely high shunts obtained in patients with SARS-CoV-2 type L (Fig. 1*A*) (8). Rather, HPV must be reversed (Fig. 2*F*(d)) with a threefold increase in blood flow to the collapsed lung regions to reach the shunt values seen in patients with COVID-19. This is exactly what has been shown using dual-energy CT in patients with SARS-CoV-2 (Fig. 2, *C* and *D*) (26–28, 84). The apparent regional vasodilation in the collapsed or edema-filled tissue was hypothesized to be caused by a dysfunctional and diffuse inflammatory process (28). As mentioned previously, it has been shown that mechanical ventilation can exacerbate perfusion abnormality by redistributing blood into poorly ventilated areas (25). A recent communication reviews the molecular factors involved in SARS-CoV-2-induced vascular pathology, including inflammation, oxidative stress, mitochondrial dysfunction, and DNA damage, which cause endothelial dysfunction, coagulopathy, and microthrombosis (23).

Physiologically Directed Treatment of SARS-CoV-2-Induced Acute Lung Injury in Patients

Noninvasive support in SARS-CoV-2.

Patients with SARS-CoV-2 acute hypoxemic respiratory failure (SARS-CoV-2-AHRF) may be refractory to oxygen and will require additional respiratory support. The choice of noninvasive respiratory support includes the use of a high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), or noninvasive ventilation (NIV). The evidence to support the use of these modalities is based on SARS, non-COVID AHRF, and ARDS data and influenced by additional factors such as the availability of ventilators and ICU beds, potential infection control issue (for patients and staff) associated with the use of high-flow open ventilation systems, and hospital capacity for oxygen and gas flows (Fig. 5).

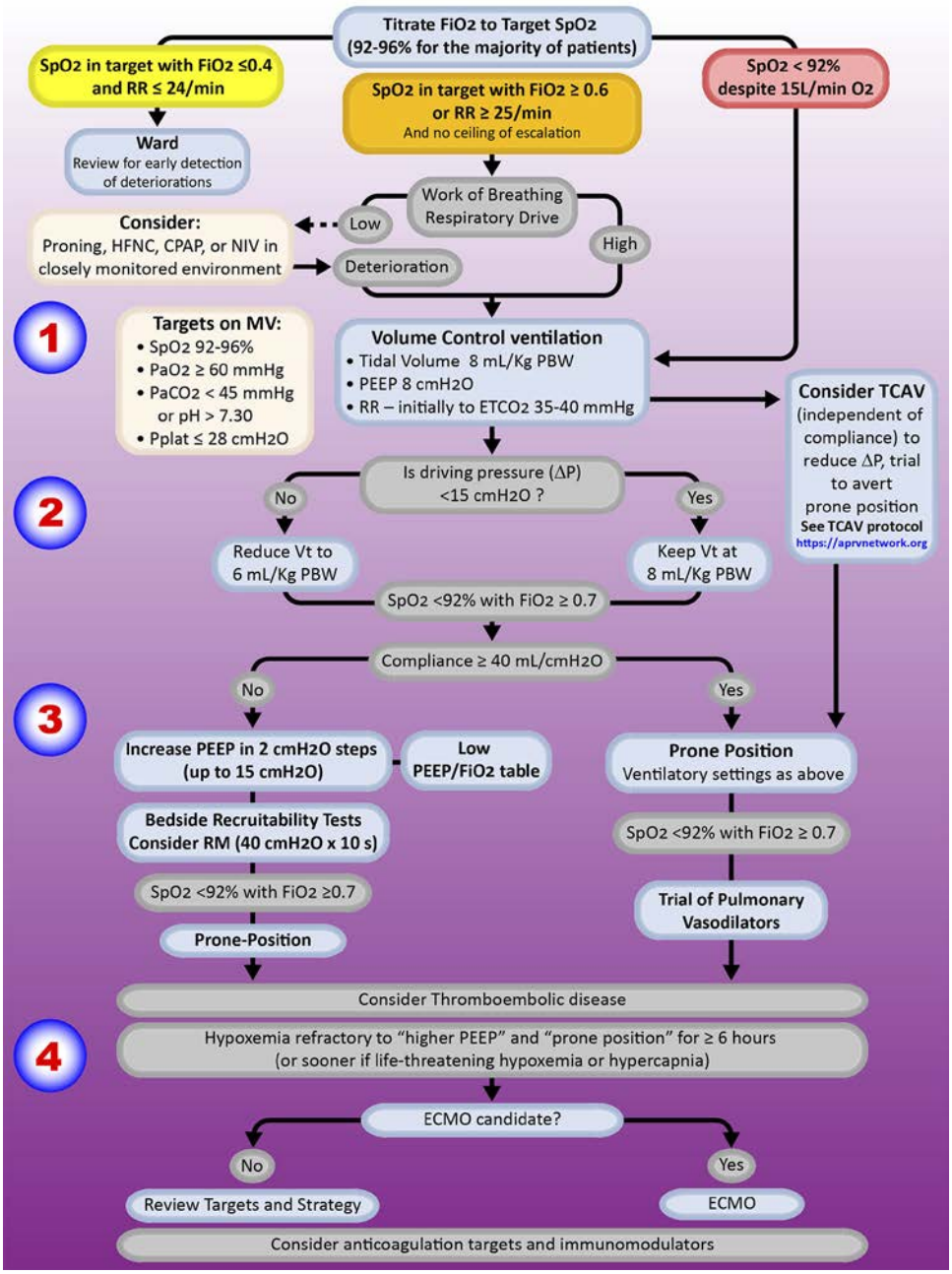

Figure 5. Illustrative flowchart for the management of respiratory failure in SARS-CoV-2. *1*: the first decision depends on the assessment of severity of hypoxemia and respiratory drive. *2*: by monitoring driving pressure, the "strain" can be estimated. Given that driving pressure is equal to tidal volume divided by compliance, and compliance is related to resting lung volume, a driving pressure >15 would indicate that the tidal volume is excessive compared with the resting lung volume and therefore indicates that the ventilatable lung is small. *3*: the assessment of static compliance will give an indication of whether hypoxemia is mainly due to altered perfusion (near-normal compliance) (Fig. 1*A*) or lung consolidation (low compliance) (Fig. 1*B*). A detailed protocol on how to set and adjust the airway pressure release ventilation (APRV) mode using the time-controlled adaptive ventilation (TCAV) method can be found on https://doi.org/10.6084/m9.figshare.12881789.v1 and https://aprvnetwork.org. *4*: early consideration for extracorporeal membrane oxygenation (ECMO) in patients who are in refractory respiratory failure.

The risks and benefits of noninvasive support in SARS-CoV-2 have been a matter of debate (85, 86): on the one hand, the use of these methods of support may reduce the risk of intubation and subsequent morbidity associated with invasive mechanical ventilation and reduce the need for ventilators, ICU beds, and staffing and possibly duration of hospitalization (these are important considerations during a pandemic). On the other hand, a high failure rate in severe ARDS has been reported (87), and the use of NIV has been associated with increased risk of intubation (88) and worse outcomes (87–89), particularly if intubation is delayed (90). High-flow oxygen through a nasal cannula in patients with acute hypoxic respiratory failure has been shown to significantly reduce mortality in a randomized controlled trial (88). More recent data in COVID-19 respiratory failure suggest that HFNC may also be effective for patients with COVID-19 in reducing invasive mechanical ventilation, although its effects on mortality are not yet demonstrated. These are important considerations, given that the durations of symptoms and hypoxemia in SARS-CoV-2 are generally longer than in other etiologies and given the scale of the pandemic.

Similarly, CPAP does not seem to reduce the need for intubation or improve outcomes (91). Data in large ARDS cohorts (92, 93) suggest that noninvasive support in patients with Pa_{O_2}/FI_{O_2} >150 mmHg is well tolerated and reduced the inspiratory effort (94). The latter point is particularly important, as patients with SARS-CoV-2 have high work of

breathing without overt dyspnea. The excessive neural drive may enhance central blood flow, increasing edema formation (95, 96), as well as the risk of lung damage through patient self-inflicted lung injury (P-SILI) (97, 98). Therefore, if the chosen noninvasive support is unable to reduce inspiratory efforts (94, 99, 100), mechanical ventilation should be applied even after resolution of hypoxemia (Fig. 5) (42, 93, 101). The "happy hypoxia" reported in patients with SARS-CoV-2 suggests that the work of breathing may be dissociated from the subjective sensation of dyspnea. This may parallel the notion that a sensation of breathlessness experienced during maximal exercise is perceived as normal, whereas a sensation of breathlessness occurring at rest may provoke anxiety and distress. Dissociation of the sensation of dyspnea may be a factor in both the lung injury and the management of patients with SARS-CoV-2, as the preserved relatively normal compliance may not engage the pulmonary and chest wall receptors in producing respiratory discomfort, with a resulting failure to appreciate mechanical loads or gas exchange abnormalities. This could be analogous to severe asthmatics who have an underappreciation of the degree of their dyspnea and appear more susceptible to near-fatal attacks (102).

Invasive Ventilation and Tidal Volumes

A flowchart of the physiologically directed treatment options for the patient with SARS-CoV-2 is seen in Fig. 5. Mechanical ventilation in ARDS aims to deliver lower tidal volume (Vt) of around 6 mL/kg predicted body weight (PBW) (103, 104) and driving pressure (ΔP) <15 cmH_2O (105, 106) regardless of Vt applied—whether low or intermediate volumes (Fig. 5) (107). This is a way of normalizing Vt to the lung volume—a proxy measure of lung strain. Given that driving pressure is the ratio between Vt and respiratory system compliance (C_{RS}) (105) and C_{RS} is proportional to the amount of aerated lung tissue, it can be understood how ΔP represents a measure of lung strain (49, 108). Thus, ΔP can be used to guide lung-protective ventilation particularly in terms of judging whether tidal volumes are too high (ΔP >15 cmH_2O) or appropriate (ΔP <15 cmH_2O) for the size of the aerated lung. However, in obese patients, the decreased chest wall compliance would alter this relationship, necessitating higher airway pressures to overcome the increased pleural pressure. One method to identify the role of the chest wall is to measure pleural pressure with an esophageal balloon and calculate the transpulmonary pressure, although many ICUs do not have this option.

In patients with well-preserved lung volume and therefore compliance [phenotype L (7), phenotype 1 (101), phenotype 4 (109)] (Fig. 1*A*), an overrestrictive Vt may not be necessary (Fig. 5). In SARS-CoV-2, driving pressures can be low (55), and therefore, lung strain and the risk of lung injury are lower than in patients with ARDS with smaller ventilatable lungs. Therefore, the selection of moderate-intermediate Vt (e.g., 8 mL/kg PBW) and lower respiratory rates can achieve a lower mechanical power and risk of VILI without increasing dead space (110, 111), hypoventilation, asynchronies, and atelectasis (Fig. 5) (42). Several studies that compared low versus intermediate Vt in both patients with and without ARDS have shown no difference in outcome between the two approaches in patients with ARDS (112, 113). In addition, Deans et al. (115) showed that 2,587 patients who were excluded from the ARMA (Lower Tidal Volume Trial) study (114) for technical reasons and received routine mechanical ventilation had an almost identical mortality (31.7% vs. 31%) as those in the ARMA LVt group (6 mL/kg). In addition, reanalysis of the ARMA data showed that patients with more compliant lungs did poorly if Vt was lowered (115).

Obviously, it is not the absolute size of the Vt that is important for lung protection but rather the size of the Vt in relation to the volume and compliance of the lung it is being delivered into. If the lung is fully opened with a near-normal compliance, a much larger Vt can be used without causing injury. Since $\Delta P = Vt/C_{RS}$ and ΔP is highly correlated with ARDS mortality (105), a high Vt would not elevate ΔP as long as the reinflated acutely injured lung was held open and kept stable with the mechanical ventilation strategy, significantly increasing C_{RS} (116).

Invasive Ventilation—PEEP

In patients with preserved lung volumes, CT chest scans tend to show small amount of lung edema or collapse (Fig. 1*A*), and therefore, response to PEEP and lung recruitability is limited (117). Ventilation with low PEEP or lower mean airway pressure is recommended (Fig. 5). CT scan and lung mechanics are important in identifying these patients, as the application of PEEP based on traditional PEEP/FI_{O_2} tables (114, 118) may lead to inappropriately high PEEP, given the discordance between the degree of hypoxemia and FI_{O_2} and the amount of potentially recruitable lung. Although the exact mechanism is unclear, these patients' hypoxemia is likely due to altered pulmonary perfusion (or microthrombosis) (Fig. 2), and therefore, a higher PEEP will increase the resting lung volume—by a quantity equal to the product of PEEP and lung compliance—and may further compromise pulmonary blood flow to the well-aerated lung, worsen right ventricular function, and cause unnecessary use of fluids or vasopressors. The PEEP volume will increase lung strain and the mechanical power to the lung (19). In these patients, the prone position may offer some temporary advantage in terms of redistribution of blood flow and improvement in Pa_{O_2}/FI_{O_2} ratio. However, these advantages may be short-lived unless there is an associated reduction in atelectasis and/or consolidation.

Since patients with COVID-19 managed with low Vt protective ventilation have a high mortality (3, 119, 120), an alternative consideration would be to use the time-controlled adaptive ventilation (TCAV) method to set and adjust the airway pressure release ventilation (APRV) mode (Fig. 5). The TCAV method is adaptive and personalized to the patient's lung pathophysiology; in the case of SARS-CoV-2 phenotype L, a near-normal lung compliance is seen (Fig. 1*A*), so that the TCAV settings will be much different from those used on patients with phenotype-H pneumonia (Fig. 1*B*) (see TCAV protocol on https://doi.org/10.6084/m9.figshare.12881789.v1 and https://aprvnetwork.org). Specifically, the high-pressure CPAP phase (P_{High}) will be higher and the release phase (T_{Low}) will be shorter in phenotype-H as compared with phenotype-L disease (see TCAV protocol supplement mentioned above) (121). Because TCAV adjustments are based on

respiratory system compliance (C_{RS}) and the slope angle of the expiratory flow curve rather than the traditional PEEP/FI_{O_2} scale, this approach is flexible regardless of C_{RS} (121–123). The dissociation between Pa_{O_2} and lung mechanics seen in SARS-CoV-2 coupled with the conventional use of the PEEP/FI_{O_2} scale may have resulted in excessive PEEP levels in patients with preserved C_{RS} (124).

The TCAV method has been successfully used as a preemptive ventilation strategy in animal experiments (125–128) and trauma patients (129) with normal C_{RS} to reduce the incidence and mortality of ARDS. Because the TCAV method has been applied successfully for rescue of refractory hypoxemia (130–132), it could also be used on patients with phenotype-H SARS-CoV-2 (Fig. 1*B*), since it a highly effective method to open and stabilize the acutely injured lung (133). However, the preferred strategy would be to use TCAV early, as soon as the standard protocol criteria for intubation are met. If these criteria are met when the patient is in phenotype L, TCAV may prevent progression to phenotype H (Fig. 1, *A* and *B*). In a recent pilot study on 10 patients with CARDS, it was shown that APRV, which was set and adjusted using the TCAV method, significantly improved Pa_{O_2}/FI_{O_2} ratio and decreased usage of vasopressors, sedatives, and analgesics. The authors concluded that "APRV may be the optimal ventilator mode" for patients with CARDS and suggested conducting a randomized controlled trial based on their preliminary data (134). Others have suggested that APRV may be a good option for patients with COVID-19, since it recruits and stabilizes the lung, increasing functional residual capacity (FRC) (135).

As the lung edema and consolidation increase over time (136), the ability to recruit lung may increase, and therefore, the Pa_{O_2}/FI_{O_2} ratio more closely represents the amount of collapsed lung (137) and lung recruitability (Fig. 1*B*) (117, 138). In this case, the use of traditional PEEP/FI_{O_2} tables (114, 118) or other methods of setting PEEP (139, 140) has a role similar to patients with ARDS from other causes. However, the TCAV method is an effective rescue strategy since it is highly effective at opening and stabilizing the acutely injured lung (130–132). The routine use of recruitment maneuvers is not recommended; however, short recruitments can be considered after assessing lung recruitability at the bedside using two PEEP levels, as the ability to recruit acutely injured lung tissue is highly variable (Fig. 5) (141, 142). The best evidence supports the use of ventilation in the prone position for 12–16 consecutive h/day (143–146). Prone positioning in SARS-CoV-2 was used in 11%–47% (41) of patients, which is higher than the use reported in the LUNG-SAFE study (Fig. 5) (16). A trial of pulmonary vasodilators may improve oxygenation and right heart function in these patients particularly if vasoconstriction of well-ventilated lung predominates (see *SARS-CoV-2-Induced Alteration of Pulmonary Perfusion*). However, the effect on outcome is uncertain.

CONCLUSION

Although many aspects of COVID-19-induced CARDS are similar to ARDS caused by other causes (bacterial, fungal, or other viruses), hypoxemia with a relatively normal lung compliance and minimal collapse of lung tissue is a distinguishing feature in some patients with COVID-19 that requires significantly different invasive ventilation strategies as discussed earlier. This novel pathophysiology has implications for management and supportive techniques currently thought to be standardized for ARDS and highlights the need for further development beyond our current gold standard, such as a more personalized approach to respiratory failure and the heterogeneity encountered clinically.

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DISCLOSURES

N.M.H. is the founder of Intensive Care On-line Network, Inc. (ICON). N.M.H. holds patents on the time-controlled adaptive ventilation method of initiating, managing, and/or weaning airway pressure release ventilation, as well as controlling a ventilator in accordance with the same, but these patents are not commercialized, licensed, or royalty producing. The authors maintain that the industry had no role in the design and conduct of the study; the collection, management, analysis, or interpretation of the data; or the preparation, review, or approval of the manuscript.

AUTHOR CONTRIBUTIONS

G.N. conceived and designed research; L.A.G. and G.N. prepared figures; N.M.H. and G.N. drafted the manuscript; N.M.H., L.C., L.A.G., and G.N. edited and revised the manuscript; N.M.H., L.C., L.A.G., and G.N. approved final version of the manuscript.

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