Pathophysiology of Hypoxemia in COVID-19 Lung Disease

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KEYWORDS

• COVID-19 • SARS-CoV-2 • Hypoxemia • ARDS

KEY POINTS

- Hypoxemia is common in coronavirus disease 2019 (COVID-19) lung disease and a prognosticator of disease severity, although challenges exist with its measurement.
- Ventilation-perfusion mismatching is the predominant cause of hypoxemia in COVID-19.
- COVID-19 lung disease leads to a wide range of pulmonary compliances, poorly correlated with degree of hypoxemia.
- Incongruence among degree of parenchymal involvement, respiratory system compliance, and hypoxemia could be explained by a diffuse pulmonary vascular process, lack of appropriate vasoconstriction in diseased regions, or both.
- The phenomenon of silent hypoxemia is best considered a consequence of the limited dyspneogenic effect of hypoxemia in comparison to mild hypocapnia and relatively normal work of breathing.

INTRODUCTION

From the beginning of the pandemic, the diagnosis and management of hypoxemia has been an essential aspect of coronavirus disease 2019 (COVID-19) care. Within the first 2 weeks after symptom onset, patients may present with increasing respiratory complaints such as cough, difficulty breathing, and exertional intolerance, which may progress to a requirement for supplemental oxygen. These symptoms are often associated with abnormalities on lung imaging, most commonly bilateral, basilar predominant ground glass opacities that may progress to consolidations. This classic pattern of COVID-19 lung disease affected most patients in the earlier waves of the pandemic,[1] although that may be changing with higher rates of vaccination, greater herd immunity from prior infection, and possibly different viral strains. Nevertheless, it remains the pattern most commonly recognized by clinicians and likely the presentation with highest morbidity and mortality.

Hypoxemia is an important prognostic indicator for patient-centered outcomes such as hospital length of stay, ICU admission, intubation, and death[2]; additionally, it may be independently associated with prolonged delays in recovery of mental status.[3] Obesity, elderly age, and underlying renal and cardiac diseases are associated more severe degrees of hypoxemia and severe COVID-19.[4] However, early in the pandemic, it was observed that the degree of hypoxemia caused by COVID-19 lung disease was poorly associated with both the severity of parenchymal involvement on computed tomography (CT) and the presence of respiratory symptoms, especially dyspnea. Additionally, early reports of intubated, critically ill patients with COVID-19 suggested a subgroup of patients in which impaired gas exchange was associated with preserved compliance, a pattern

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purportedly unique to COVID-19.[5] These reported mismatches between degree of hypoxemia and other markers of severity spawned great confusion and a search for new pathophysiologic mechanisms unique to COVID-19 infection. However, as our understanding of COVID-19 epidemiology has grown, it has become clear that many of these paradoxic findings are likely the consequences of relevant but often-forgotten tenets of respiratory physiology, potentially magnified by specific features inherent to COVID-19 pathophysiology and epidemiology.

Challenges with Interpreting Hypoxemia in COVID-19

The challenge with interpretation of the severity of hypoxemia in COVID-19 lies firstly in the heterogeneity of the underlying patient population; many of the physiologic studies noted above included patients at varying time points in their disease course, with different underlying comorbidities and severity of disease, and especially on different respiratory support settings. This latter point becomes particularly important when using P_aO_2/F_iO_2 to describe hypoxemia. Although this ratio should ideally provide some comparable indication of disease severity, in actuality, it is strongly influenced by the degree of venous admixture and cardiac output in the individual patient, both of which are highly affected by positive end-expiratory pressure (PEEP); for example,[6] P_aO_2/F_iO_2 ratios are highly variable even in the same patient when compared before and after the use of mechanical ventilation, suggesting that its use to prognosticate in spontaneously ventilation in patients with COVID-19 (especially those on high-flow nasal cannula) is limited.[7]

Others have recommended the use of alternative (and less invasive) options for prognostication, such as the respiratory rate-oxygenation index, based in part of oxygen saturation rather than P_aO_2.[8] However, it is well known that pulse oximetry becomes quite inaccurate in comparison to arterial blood samples at saturations less than 75% to 80%, depending on device quality.[9] Moreover, perhaps more importantly, it has become clear during the course of the COVID-19 pandemic that pulse oximeters may also routinely overestimate oxygen saturation measurements in mild-moderate hypoxemia, especially in patients with darker skin tone. One study of paired samples of arterial oxygen (S_aO_2) and pulse oximetry (S_pO_2) saturations found an overall average difference of 1.4%; however, when restricted to the group with S_aO_2 85% to 89%, the difference was 2.8%, and up to 3.9% in Black and 5.8% in Asian patients.[10] Rates of occult hypoxemia from pulse oximetry (defined as S_aO_2 <88% despite S_pO_2 92%–96%) may be as high as 30% in Asian, 29% in Black, and 30% of Hispanic patient populations, as compared with 17% in Caucasian patients.[11] These discrepancies in saturation data highlight the challenges associated with accurately measuring hypoxemia in COVID-19 lung injury, especially among certain ethnic groups at highest risk for severe disease.

Pathogenesis of Hypoxemia in COVID-19

COVID-19 infection is known to cause acute damage to the alveolar-capillary barrier, involving damage to both alveolar epithelium and capillary endothelium; this injury is directly viral-mediated or due to the consequent inflammatory response.[12] Lung histology in nonsurvivors suggest that COVID-19 pathologic condition generally mimics that of classic ARDS, with diffuse alveolar damage and consequent formation of hyaline membranes.[13] Less severe or prolonged cases of COVID-19 lung injury in survivors may suggest organizing pneumonia, which is thought to represent an aberrant parenchymal recovery process after acute injury.[14] Importantly, COVID-19 autopsy studies often reveal significant capillary endothelial injury and intracapillary thrombosis, similar to classic ARDS although perhaps at a greater prevalence.[15] The mechanisms by which viral-mediated and immune-mediated damage occurs to endothelial and epithelial membranes is beyond the scope of this article; nevertheless, there is likely an interplay between vascular effects from endothelialitis and thrombosis, and direct or indirect alveolar injury leading to alveolar filling.

Physiologically, the 5 causes of hypoxemia are (1) low partial pressure of inspired oxygen, (2) alveolar hypoventilation, (3) diffusion limitation, (4) ventilation-perfusion mismatching (and specifically low ratios of ventilation/perfusion, or V_A/Q), and (5) right-to-left shunt. Of these causes, only ventilation/perfusion mismatching and pure right-to-left shunt lead to hypoxemia in ARDS, as measured by the multiple inert gas elimination technique (MIGET).[16] Traditionally, pure right-to-left shunt through nonventilated lung regions has been considered the predominant cause of hypoxemia in classic ARDS, perhaps because those patients studied via MIGET had predominant findings of significant consolidation on lung imaging, with relative sparing of other lung regions (the overall reduced volume of normal parenchyma being known as “baby lung”).[16] However, this pattern may not hold true for all cases of lung infection, especially early in the disease course when

consolidations are often absent.[17] Additionally, the degree of venous admixture from low V_A/Q regions will increase in the context of a high cardiac output, often seen in both COVID-19 lung disease and non-COVID-19 ARDS.[18]

MIGET studies have not yet been performed in COVID-19 lung disease to our knowledge; however, in the absence of such direct testing, computational models of ventilation and perfusion associated with high-resolution CT have yielded interesting findings. In computational models of V_A/Q mismatch and shunt physiology, based on CT imaging and markers of gas exchange in severe COVID-19 lung disease, it has been suggested that the degree of hypoxemia cannot be solely due to shunt through nonaerated regions, such that low V_A/Q units are additionally responsible.[19] In such models with small fractions of nonaerated or poorly aerated lung parenchyma, significant hypoxemia could be explained by either significant hyperperfusion of nonaerated lung regions, or alternatively due to the presence of ventilation/perfusion mismatch in aerated lung regions through a diffuse vascular process such as endothelialitis or microthrombosis.[20]

Regional Ventilation-Perfusion Mismatch in COVID-19 Lung Disease

The 2 predominant theories that could explain the findings of the computational models described above are the presence of diffuse pulmonary vascular endothelialitis and thromboembolism (leading to hypoperfusion in relatively preserved lung regions) and vascular dilation not responsive to normal hypoxic pulmonary vasoconstriction (HPV, leading to hyperperfusion in poorly aerated or nonaerated lung regions). These theories are certainly not mutually exclusive; indeed, several cross-sectional imaging studies, including techniques for measuring regional perfusion, have provided support for both theories.

For example, subtraction CT angiography with iodine mapping demonstrates that hypoperfusion of apparently healthy lung parenchyma is common, with more severe perfusion abnormalities associated with lower P_aO_2/F_iO_2 ratios and more likely to require invasive mechanical ventilation.[21] Similarly, dual energy computed tomography (DECT) in COVID-19 lung disease has revealed mosaic perfusion patterns in the absence of macroscopic pulmonary embolism, and not clearly matched by pulmonary opacities, strongly arguing in favor of a diffuse pulmonary microvascular process.[22] Indeed, diffuse endothelialitis and microvascular thrombosis are commonly found on autopsy in COVID-19,[23] even in the setting of therapeutic anticoagulation.[24] However, pulmonary vascular abnormalities and hypercoagulability are also well documented in non-COVID-19 ARDS.[25] Although some therapeutic trials have suggested improvements in oxygenation with empiric initiation of therapeutic anticoagulation in patients with COVID-19, especially those with increased dead space fraction,[26,27] this finding has not been reproduced in larger trials.[28–30]

Other imaging studies suggest abnormal hyperperfusion in areas of parenchymal involvement. Understandably, lung aeration loss is strongly associated with lower P_aO_2/F_iO_2 ratios, mostly due to gas–blood volume mismatch noted on DECT.[31] Peripheral vessel dilation is noted in almost two-thirds of mechanically ventilated patients undergoing DECT, involving almost half of the lung parenchyma,[23] with an interesting pattern of "vascular tree-in-bud" abnormalities correlating with increased dead space, prolonged hospitalization, and need for mechanical ventilation. Although some groups have noted abnormally dilated pulmonary vessels adjacent to areas of parenchymal involvement,[32] which could suggest a sort of locoregional perfusion abnormality, this has not been reported in other studies.[33] Therapeutic maneuvers to improve ventilation-perfusion matching, including inhaled pulmonary vasodilators and almitrine (which may act to augment HPV) have demonstrated improvements in oxygenation in patients with COVID-19,[34] although these same benefits have been described previously in non-COVID ARDS without a survival benefit.[35,36] Finally, ventilation-perfusion mismatching and hypoxemia may develop via abnormal intrapulmonary shunts in COVID-19. Physiologically, the presence of such shunts is suggested by the appearance of microbubbles in the systemic circulation based on transcranial Doppler imaging[37] and in up to 16% of patients on echocardiography.[38] They have also been demonstrated radiographically at the level of the secondary pulmonary lobule on CT reconstructions,[39] and on autopsy in severe COVID-19 lung disease.[40] However, it should be noted that the presence of such shunts has been reported in a subset of non-COVID ARDS undergoing echocardiography, suggesting that this process is likely not unique to COVID-19 lung injury.[41]

Are there specific pathophysiologic factors unique to COVID-19, which cause a greater degree of ventilation-perfusion mismatch, such as a virally-mediated impairment of HPV? One theory posits that binding of ACE-2 receptors by SARS coronaviruses in pulmonary vascular endothelium leads to downregulation of these receptors and abrogation of normal vasoregulation in these regions.[42] Indeed, ACE-2 inhibition by lisinopril has

previously been shown to attenuate hypoxic pulmonary vasoconstriction.[43] Although this theory is intriguing, the renin-angiotensin-aldosterone system remains a minor contributor to pulmonary vasoregulation in comparison to the release of local mediators (endothelin, prostacyclin, and nitric oxide), which could be affected by direct viral injury to pulmonary artery endothelial cells.[15] At this time, there is no clear evidence supporting a direct impact of SARS-CoV-2 infection on local mechanisms of HPV.[44] However, even in the absence of direct modulation by viral infection, local and systemic inflammatory responses to infection can significantly attenuate HPV responses in animal models.[45] Finally, opening of preexisting intrapulmonary bronchopulmonary anastomoses could provide a unifying explanation for abnormal ventilation-perfusion matching, without invoking a direct effect on HPV.

Hypoxemia and Respiratory Mechanics in COVID-19 Lung Disease

Multiple large observational studies have demonstrated a broad unimodal distribution of respiratory system compliance (C_{RS}) in COVID-19 ARDS. The overall clinical data suggest that C_{RS} in COVID-19 lung injury has a wide range across studies (20–90 mL/cmH_2O),[46–50] not dissimilar to pre-COVID ARDS cohorts.[51,52] Based in part on these accumulated data, clinical practice guidelines[53] and most experts[54] agree that equivalent ventilatory strategies be used for both COVID-19 and non-COVID-19 forms of ARDS, especially the routine use of lung protective ventilation. One explanation for the high heterogeneity in compliance is the presence of a predominant vascular pathologic condition, as discussed previously. Proponents of this theory point to the high dead space fractions and ventilatory ratios calculated from many patients with COVID-19.[55,56] Indeed, high ventilatory ratios (a marker of increased dead space) are associated with elevated levels of D-dimer and areas of hypoperfusion on CT pulmonary angiograms.[57] However, it is important to mention that dead space ventilation does not directly contribute to hypoxemia, but rather can cause concomitant hyperperfusion and low V_A/Q in other regions, as is classically noted in pulmonary emboli.[58] Additionally, calculations of dead space fraction that rely on measurement of arterial CO_2 and estimation of alveolar CO_2 (the Enghoff modification to the Bohr equation for dead space fraction) will not correct for decreased CO_2 elimination in areas of shunt, and thereby overestimate dead space.[59] Ventilatory ratios have been variably associated with degree of hypoxemia in COVID-19 lung disease, and this association can change during the course of disease.[4,57,60,61]

An alternative reason for the heterogeneity of compliance, which seems quite likely, is that compliance changes as COVID-19 lung disease progresses. For example, in cohorts of COVID-19 ARDS in which preserved compliance has been described, there is a clear negative correlation between compliance and number of days since symptom onset[62]; perhaps early intubation due to concerns with viral transmission played a large role in these findings. Indeed, in other groups, prolonged time to intubation[63,64] or prolonged duration of symptoms[49] are associated with worsened compliance, suggesting a later stage in the disease, although patient self-inflicted lung injury (hypothesized to occur during spontaneous ventilation in the setting of acute lung injury and impaired compliance) could conceivably be implicated.[65] The presence and severity of obesity has also been implicated as a potential explanation for the heterogeneous compliance values noted in COVID-19 lung disease. However, although it contributes to alveolar derecruitment, obesity does not seem to significantly affect overall respiratory system compliance. Esophageal balloon measurements demonstrate that elevated body mass index (BMI) is associated with elevated end-expiratory pleural pressures but normal chest wall compliance, and in these patients, lung compliance correlates poorly with P_{aO_2}/F_{iO_2} ratios.[66]

How do respiratory mechanics correlate with degree of hypoxemia in COVID-19? A positive, although relatively weak, correlation has been noted between compliance and degree of hypoxemia,[50,67] although this is not universal.[57,66] In one study, compliance and oxygenation were not initially correlated on day 1 of intubation but there was a strong positive correlation by day 7,[61] suggesting progression of parenchymal injury and nonaerated lung regions; however, other longitudinal studies have not reproduced this finding.[4] Recruitability, or the ability of nonaerated or poorly aerated lung parenchyma to be reopened with additional PEEP, is similarly variably associated with the severity of hypoxemia before recruitment.[49,61] Surprisingly, even with significant interindividual variability, recruitability does not seem to predict oxygenation response to increases in PEEP.[50,68] This seems counterintuitive if considering that the mechanism of improved oxygenation with increased PEEP is by recruitment of previously nonventilated alveoli. However, increased PEEP may also cause a decrease in cardiac output and resultant pulmonary blood flow to nonrecruitable alveoli. Although this effect remains poorly understood in COVID-19 and ARDS in general, it may

be related to partial correction of an underlying hyperdynamic pulmonary circulation in the setting of impaired hypoxic vasoconstriction.[16,69]

Similarly, prone positioning may improve oxygenation in COVID-19 not by improving overall compliance but through a mix of posterior recruitment and ventral derecruitment[70]; this allows for greater homogenization (and therefore matching) of ventilation and perfusion throughout.[71]

Most studies in intubated patients with COVID-19 have noted an average improvement in oxygenation with prone positioning even in the absence of a change in respiratory system compliance,[72–74] which seems to persist after resupination.[75] However, prone positioning does not always lead to better oxygenation, with one large study noting improved P_aO_2/F_iO_2 in only 45% of intubated patients with COVID-19 after proning.[76] Although prone positioning in nonintubated patients likely improves oxygenation transiently and may delay the need for intubation,[77] the effect seems to be mostly reversible on resuming supine positioning.[78,79]

Hypoxemia and Respiratory Symptoms in COVID-19 Lung Disease

From very early in the COVID-19 pandemic, clinicians reported a subset of patients presenting with COVID-19 lung disease causing hypoxemia but in the absence of concomitant respiratory symptoms such as dyspnea. This syndrome, most commonly referred to as "silent hypoxemia," was seemingly unique and not previously described in the medical literature. Indeed, it is difficult retrospectively to find evidence of silent hypoxemia in previous cohorts of acute lung injury, or to dissociate symptoms of acute lung injury from those of the underlying insult itself, such as pneumonia, sepsis, or trauma. There is likely a strong ascertainment bias at work when considering the prevalence of silent hypoxemia in COVID-19 infection, given the ability to accurately detect cases at early stages or even before lung disease develops, as compared with many other causes of acute lung injury. However, prior case series of virally-mediated causes of acute lung injury, notably infection by SARS-CoV-1, reported the absence of dyspnea in up to a quarter of patients, suggesting at least some degree of silent hypoxemia could have been present in earlier epidemics.[80,81]

Nevertheless, the absence of dyspnea is common at the time of hospitalization for COVID-19, occurring in up to 65% of patients in one study of hospitalized patients, most of whom had evidence of lung disease on CT.[82] The prevalence of silent hypoxemia specifically has varied widely by study, ranging between 9% and 36%, in part, due to reporting biases and the lack of a universal definition.[46,48,83,84] In one large cohort of patients admitted with COVID-19 lung disease and acute respiratory failure (of whom 83% required either supplemental oxygen or ventilatory support on presentation), lack of dyspnea was reported in 36%.[84] In another cohort, dyspnea was absent in 13% of patients with COVID-19 presenting with arterial oxygenation saturation less than 90%.[85] The frequency of dyspnea at presentation in later strains of COVID-19 is not well described and difficult to estimate, in part, due to the high efficacy of vaccination; however, it has been noted that hospitalization rates in Delta and Omicron waves were not lower than the initial Alpha wave among unvaccinated patients.[86] It is also likely that the prevalence of silent hypoxemia varies significantly based on time of presentation, severity of illness, or presence of comorbidities known to be associated with severe disease such as elderly age, obesity, and diabetes mellitus.[87] Patients with silent hypoxemia may present earlier after symptom onset to medical attention, and often for nonrespiratory complaints, suggesting that this may represent an earlier time point in their disease course before the onset of respiratory symptoms.[88] Although it likely delays the use of respiratory support, it remains unclear to what extent silent hypoxemia leads to worse clinical outcomes, with studies suggesting equal, better, or worse outcomes as compared with symptomatic hypoxemia.[82,85,89]

There was considerable interest initially in the possibility of reduced hypoxic ventilatory response (HVR) in patients with COVID-19, in part due to the neurotropic manifestations commonly recognized in COVID-19 infection such as olfactory dysfunction and high rates altered mental status during severe disease. However, although HVR has never been formally tested in patients with COVID-19 and can vary widely in the healthy population,[90] the almost universal presence of hypocapnia in patients presenting with hypoxemia argues against the presence of a reduced ventilatory response. For example, in one series of patients with mildly symptomatic COVID-19 and hypoxemia, calculations of alveolar CO_2 correlated against arterial oxygen suggested that alveolar ventilation was increased between 1.1-fold and 1.7-fold as compared with known values for healthy controls undergoing formal HVR testing.[91] Indeed, elevated respiratory rates are often anecdotally noted in patients with COVID-19 not describing dyspnea, with one study describing a median respiratory rate of 31 breaths per minute in the 5% of its cohort with silent hypoxemia.[87] In another cohort of 45 patients

admitted to a respiratory unit for COVID-19, the average $Paco_2$ was 32 mm Hg, with significantly lower Borg dyspnea scores in the COVID-19 population as compared with non-COVID patients admitted during the same time period (although the control group had a significantly increased rate of underlying lung disease and hypercapnia).[92] However, it must be noted that another group found a lower ratio of oxygen saturation to respiratory rate in patients with COVID-19 as compared with historical controls; without blood gas analysis, it is impossible to know if hypocapnia (which blunts HVR) could help to explain this finding.[93]

In the absence of demonstrable hypoventilation, the best explanation for silent hypoxemia invokes the common characteristics of COVID-19 lung disease described in this article correlated with the known physiologic basis for ventilatory drive. First, it must be noted that hypoxemia is a very weak stimulant for increased ventilation and for the onset of dyspnea, as compared with increased work of breathing or hypercapnia[94]; and in fact, increased ventilation may occur in mild-to-moderate hypoxemia even without patients noting dyspnea.[95] Early COVID-19 may otherwise lack strong dyspneogenic stimuli, such as increased work of breathing due to poor compliance or high airway resistance. Second, increased ventilation in an asymptomatic patient, in turn, will efficiently eliminate CO_2, given a presumed low-normal work of breathing and at least some regions of retained ventilation-perfusion matching. Thus, the mild stimulant effect of hypoxemia will be more than outweighed by hypocapnia, which significantly suppresses ventilation and which has been observed frequently in the silent hypoxemia cohorts described above. Furthermore, respiratory alkalosis per se is known to attenuate HPV responses.[45] Finally, hypoxemia caused by mismatches in ventilation and perfusion are not corrected by increased ventilation, such that hypoxemia will be persistent. Thus, silent hypoxemia is most probably the result of a combination of factors: poorly aerated, hyperperfused lung regions with retained compliance, the weak dyspneogenic effect of hypoxemia counterbalance by the resultant hypocapnia from mild hyperventilation, and the inability of increased ventilation to correct hypoxemia due to these low V_A/Q regions.

SUMMARY

A practical effect of the immense amount of research produced in describing gas exchange abnormalities in COVID-19 lung disease has been to reiterate the importance of basic respiratory physiology in making sense of novel causative agents of lung injury. Impairment of ventilation-perfusion matching is the hallmark of any lung disease associated with gas exchange abnormalities, regardless of parenchymal or vascular predominance, and the range of mismatch does not seem to be unique to the effect of SARS-CoV-2. Although studies remain to be done, especially in terms of understanding the interplay between vascular and alveolar injury during the course of COVID-19 and the potential for direct viral mediation of hypoxic pulmonary vasoconstriction, the preponderance of the current evidence suggests that the effect of COVID-19 infection on gas exchange is well explained by established tenets of respiratory physiology and should not preclude the use of standard treatments for acute lung injury.

CLINICS CARE POINTS

- Hypoxemia is a prognosticator of disease severity in COVID-19 lung injury; however, inaccuracy in measurement through pulse oximetry (especially among non-Caucasian patients) is an important obstacle to early risk stratification and equitable treatment decisions.
- The predominant cause of hypoxemia in COVID-19 is the presence of lung regions with a low ventilation/perfusion ratio, although right-to-left shunting through consolidated lung regions also contributes, especially as the disease progresses.
- Theories to explain the degree of ventilation-perfusion mismatch include a diffuse pulmonary vascular process, which limits perfusion to normally aerated regions, and overperfusion of nonaerated areas, either due to loss of normal vasoconstrictory responses or potentially the effect of intrapulmonary bronchopulmonary anastomoses.
- Hypoxemia in COVID-19 lung disease is poorly correlated with both pulmonary compliance and recruitment responses to increased PEEP.
- Prone positioning may help to homogenize ventilation and perfusion and improve oxygenation in COVID-19, similar to its effect on gas exchange in non-COVID-19 ARDS.
- In the absence of any clear evidence of a virus-specific effect on ventilatory control, the phenomenon of silent hypoxemia is best understood because of the limited dyspneogenic effect of hypoxemia in comparison to the mild degree of hypocapnia and relatively normal work of breathing commonly noted in such patients.

DISCLOSURE

Dr Swenson and Hardin have no disclosures relevant to this article.

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