

“Silent” Presentation of Hypoxemia and Cardiorespiratory Compensation in COVID-19

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The Coronavirus infection disease 2019 (COVID-19) pandemic is bringing unprecedented numbers of patients with significant hypoxemia to medical care. It is critical that clinicians caring for hypoxemic patients recognize two facts: (1) it is common for hypoxemia to exist without dyspnea (“silent hypoxia”); and (2) while patients may initially achieve cardiorespiratory compensation to hypoxemia, this compensation can fail precipitously. The spectrum of variability in human responses to hypoxemia is striking, influenced by differences in respiratory drive (the hypoxic ventilatory response) related to age, medications, coexisting diseases and genetic background. Healthy individuals usually respond to acute hypoxemia with dyspnea, but because of hypoxic suppression of dyspnea (hypoxic ventilatory decline) and hypocarbic suppression of dyspnea, profound hypoxemia can be minimally symptomatic (“silent”), or noticed only during exertion. Cardiovascular compensation for hypoxemia is similarly variable, with the normal responses of tachycardia and increased cardiac output limited by age, genetics, and coexisting disease. Failure to compensate for decreased oxygen transport is signaled by lactic acidosis, bradycardia, and decreased cardiac output. The latter may develop rapidly, and all are indicators of impending tissue injury or death from hypoxemia.

Articles in the popular media^{1,2} and even a few in medical journals^{3,4} have stated that the symptoms of hypoxemia in COVID-19 are unique, with minimal dyspnea or cognitive depression despite oxygen saturations measured by pulse oximetry of less than 70%. Based on decades of studies with healthy volunteers and controlled, severe hypoxemia at the University of California at San Francisco Hypoxia Research Laboratory and during high-altitude medical research expeditions, it is our experience that while a lack of dyspnea in response to hypoxemia is not typical, it is commonly observed.

There are several reasons that healthcare providers may be surprised by apparently well-tolerated hypoxemia. First, are several fundamentals related to the regulation of breathing and the sensation of dyspnea: the suppression of respiratory drive by the dual effects of reduced carbon dioxide (hypocarbica), as well as by hypoxemia itself (hypoxic ventilatory decline). Simultaneously, even during severe hypoxemia,

cognition can be preserved by autoregulation of cerebral blood flow and brain oxygen delivery.

Another broadly held false belief brought into focus by the COVID-19 pandemic is that hypoxia alone causes tissue injury. This is rarely the case; rather, acidosis and damage develop when cardiovascular compensation fails, critically reducing blood flow and oxygen delivery either globally or to particular organs.^{5,6} The critical contribution of cardiovascular compensation to clinical outcome is supported not only by a large body of experimental evidence, but also by our own experience as anesthesiologists, intensivists, and scientists studying hypoxia in human subjects.

The purpose of this focused review is to describe human response to severe hypoxemia, focusing not on the pathophysiology of lung injury but on the respiratory system response to hypoxemia. In addition, we summarize current knowledge of the features and limits of human cardiorespiratory response and adaptation to profound hypoxemia and describe some of the critical parameters that can help identify when adaptive compensation is failing.

Degree of Hypoxemia and Lung Injury in Hospitalized Patients with COVID-19

The available information about the pathophysiology of SARS-2 CoV pneumonia suggests that while key features of the disease are more pronounced than in other viral pneumonias, the pathophysiology is not unique.

The cardinal reason for hospital admission in COVID-19 positive patients is hypoxemia.⁷⁻⁹ Although younger patients with no prior history of lung disease can have severe pneumonia and require invasive ventilation, elderly patients are at especially high risk for severe hypoxemia, with mortality rates of 40 to 80% reported in various cohorts.^{8,10-12} Preexisting comorbid conditions, including cardiovascular disease, diabetes mellitus, and chronic lung disease, as well as male sex and obesity, also confer higher risk of severe disease and poor outcomes.^{8,10-12}

Hypoxemia is a leading predictor of admission to the intensive care unit, mechanical ventilation, and death.^{12,13} Arterial blood gas and oxygen saturation (pulse oximetry) data often show severe hypoxemia at time of presentation, with wide alveolar-arterial P_{O_2} gradients and low PAO_2/F_{IO_2}

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ratios. Increased oxygen requirements have been addressed with increased use of noninvasive oxygen therapy (including high flow nasal oxygen), prone positioning, invasive ventilation, and in some cases, extracorporeal membrane oxygen. Hypercarbic respiratory failure has not been a prominent presenting feature in existing reports or in our experience at University of California at San Francisco.

Intrapulmonary shunt and ventilation/perfusion mismatch are the chief gas exchange abnormalities causing hypoxemia in COVID-19, as they are in other viral pneumonias, bacterial pneumonias,¹⁴ and acute respiratory distress syndrome.¹⁵ However, some features of COVID-19 may be more pronounced than in other viral pneumonias, including substantial endothelial damage and micro-/macro-emboli formation.¹⁶ Limitation of diffusion across the alveolar membrane can cause hypoxemia, but while this is seen in humans at high altitude due to low inspired and alveolar P_{O_2} ,¹⁷ in patients with loss of functional lung units (such as in interstitial lung disease or emphysema), and in some elite athletes at extremely high levels of cardiac output¹⁸ it does not significantly contribute to hypoxemia in ARDS.¹⁵ Unique to shunt physiology is that increased ventilation decreases carbon dioxide more than it increases oxygenation. The reduced carbon dioxide limits respiratory drive and dyspnea (fig. 1).

Although intrapulmonary shunt is the dominant presenting gas exchange abnormality in COVID-19, dead space may significantly worsen with progression of ARDS. Hypoxemia that does not resolve with supplemental oxygen clearly indicates that gas exchange impairment has progressed beyond ventilation/perfusion ratio (V/Q) mismatch and includes substantial intrapulmonary shunt. Alveolar filling, a cardinal feature of ARDS, correlates with lung radiographs and impaired gas exchange. Of note, the pathophysiology of ARDS is different from that of high-altitude pulmonary edema, in that COVID-19 involves an inflammation mediated alveolar fluid leak and that of high-altitude pulmonary edema is related to elevated transcapillary pressure.¹⁹

The mechanisms by which COVID-19 produces ARDS that affects large proportions of lung parenchyma may involve both a reduced innate immune response and an exaggerated inflammatory cytokine response ("cytokine storm").²⁰ While the novelty of this pattern of immunologic disturbance is debated,²¹ the impacts on pulmonary gas exchange do not appear to be unique. The known physiology of viral pneumonia and ARDS involves well characterized disturbances that produce intrapulmonary shunt, ventilation-perfusion mismatch,²² increased dead space ventilation, and decreased compliance.²³ Profound gas exchange abnormalities persist after initiation of high-flow nasal oxygen or invasive ventilation despite lung protective ventilator protocols, prone positioning, and maximal F_{IO_2} .^{8,24,25} As with other pneumonias, some patients maintain near normal lung compliance, and others

suffer decreased compliance as disease progresses,²⁶ representing a diversity of pathology.²⁷ Appropriate management of invasive ventilation in ARDS has been recently reviewed and no strong data exist to support modification of existing ARDS protocols for COVID-19.^{28,29} Readers are referred to the frequently updated consensus statements concerning treatment of COVID-19 by the World Health Organization: (<https://www.who.int/publications/i/item/clinical-management-of-covid-19>).

Hypoxemia and Breathlessness: Variability in Humans

Hypoxemia can present in a highly variable manner, with some patients dyspneic with labored breathing and panicked, and others calm, despite oxygen saturations in the 70% range or below. The processes that produce intrapulmonary shunt do not necessarily decrease lung compliance or produce dyspnea. For many hypoxemic patients, oxygen saturations less than 70% can be tolerated for some time with only moderate and transient alterations in mentation or other signs and symptoms.³⁰ Dyspnea may only occur with exertion, although decreased exercise tolerance is a nonspecific symptom in acute illness. Decreased lung compliance contributes to dyspnea, but as previously discussed, early COVID-19 pneumonia may present with shunt and normal lung compliance.²⁶ In our experience with profound experimental hypoxemia to oxygen saturations as low as 50% in healthy humans, subjective symptoms of hypoxia may go unnoticed in some individuals, with no appearance of discomfort and minimal hyperpnea.³⁰ Given this variability in individual responses to hypoxemia, it is not surprising that some COVID-19 patients have been described as asymptomatic "silent" or "happy hypoxia."³ Tobin *et al.* recently reviewed some of the factors accounting for reduced dyspnea in COVID-19 patients.⁴

One of the key reasons that COVID-19 patients may not present with marked dyspnea is that the main gas exchange abnormality involves shunt. Intrapulmonary shunt and V/Q mismatch has minimal effects on carbon dioxide excretion compared to oxygen uptake.³¹ Thus, even mild hyperventilation is capable of significantly reducing arterial carbon dioxide and decreasing respiratory drive mediated by both the carotid and central chemoreceptors³² (fig. 1). Carbon dioxide retention is more strongly correlated with breathlessness in lung disease than is hypoxemia.³³ In patients who can increase breathing and lower arterial partial pressure of carbon dioxide, breathlessness will be limited.³⁴ This is similar to what is experienced by most people on ascent to high altitude: arterial hypoxemia is present but subjective breathlessness is limited by subtle, often unnoticed increases in the respiratory rate that helps the lungs "blow off" enough arterial carbon dioxide to mitigate the sensation of dyspnea.³⁵

Breathing responses to hypoxia are experimentally quantified by the hypoxic ventilatory response,³⁶ a response largely mediated by the carotid chemoreceptors. The

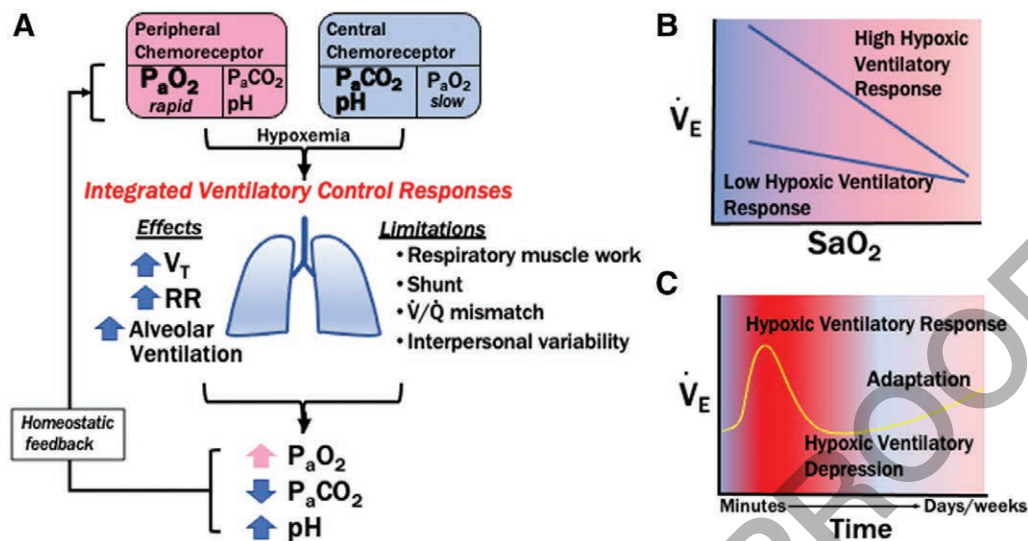


Fig. 1. Sensation of and response to arterial hypoxemia. (A) Hypoxemia is sensed primarily at the carotid body (“peripheral”) chemoreceptors, and the gain of the carotid body response to hypoxia is increased by increasing P_{aCO_2} and decreasing pH. The central chemoreceptors, located on ventral medulla, primarily sense CO_2 and pH, but are slowly modulated by hypoxemia. Increased ventilation decreases P_{aCO_2} , limiting the increased respiratory drive and subjective dyspnea from hypoxemia. In COVID-19, gas exchange at time of presentation is primarily impaired by shunt and \dot{V}/\dot{Q} mismatch, which worsens oxygen exchange, while P_{aCO_2} is relatively normal or reduced. Subjective sensation of dyspnea in shunt physiology is limited compared to lung pathology involving increased work of breathing due to increased lung water or interstitial thickening.⁶⁴ (B) The output of central and peripheral ventilatory control centers varies with innate sensitivity to hypoxemia, in the form of the hypoxic ventilatory response, defined as the slope of the increase in minute ventilation during desaturation, which is essentially linear. Different individuals may have a robust or muted hypoxic ventilatory response. (C) Ventilatory response to hypoxemia is time dependent, exhibiting a roll-off or decline (hypoxic ventilatory decline) within 15 to 20 min of hypoxemia. Breathing becomes progressively periodic with worsening oxygenation⁴⁶. RR, respiratory rate; \dot{V}/\dot{Q} , ventilation/perfusion ratio; V_T , tidal volume;

hypoxic ventilatory response in humans is highly variable: some will greatly increase the respiratory rate and tidal volume when exposed to hypoxia while others will have little response³⁷ (fig. 1B). Breathing responses to both hypoxia and hypercapnia (the hypercapnic ventilatory response) are also significantly reduced in older adults. Multiple studies have found 40 to 50% reductions in the hypoxic and hypercapnic ventilatory responses between young (22 to 30 yr) and older (64 to 73 yr) subjects.^{38,39} Hypoxic ventilatory response varies with ethnicity³⁷ and is blunted by chronic hypoxia, as in chronic obstructive pulmonary disorder and sleep apnea, as well as in obesity,^{40,41} placing these patients at higher risk of more profound hypoxemia at time of clinical presentation.

Impairments in Oxygen Uptake Caused by Profound Hypoxemia

Blunting of the hypoxic ventilatory response during prolonged hypoxemia is another factor that can exacerbate existing hypoxemia. Hypoxic ventilatory decline is mediated by the brainstem and cerebrocortex, producing decreased minute ventilation despite significant hypoxemia.^{37,42} Hypoxic ventilatory decline appears within about 15 min

of sustained hypoxemia and could be present in any patient presenting with hypoxemia due to COVID-19. In addition, hypoxic ventilatory decline, by decreasing chemoreceptor sensitivity to hypoxemia would decrease breathlessness (fig. 1, A and C). Although hypoxic ventilatory decline is overcome during healthy adaptation to hypoxia as in ascent to high altitude,³⁵ this adaptation fails in chronic mountain sickness and results in worsening hypoxemia, polycythemia, and in severe cases congestive heart failure.⁴³

Profound hypoxemia produces irregular or periodic breathing that causes minute-to-minute fluctuations in oxygenation in both sleep and awake states.^{44,45} This is observed in both pneumonia and in high altitude hypoxia, and at sea level with hypoxic air breathing.⁴⁶ These fluctuations require continuous pulse oximetry to capture the variation and to discern the overall trajectory of saturation values: noting only single values on a digital display may lead to over- or underestimate the degree of hypoxemia. A treating clinician should be aware that the profound hypoxemia noted in COVID-19 may represent a temporary nadir in oxygen saturations that are constantly varying.

Hypoxemia can increase the severity right-to-left shunt by elevating pulmonary artery pressures, increasing blood

flow through a patent foramen ovale or other venous channels. Shunting through a patent foramen ovale is observed in about 15% of normal subjects during acute hypoxemia during breathing hypoxic air mixtures to saturations of 70 to 80%. It is also seen during exercise at high altitude. This added intracardiac shunt may worsen hypoxemia out of proportion to the apparent lung injury. Furthermore, because shunt and decreased mixed venous PO_2 shift gas exchange to the steep portion of the oxyhemoglobin dissociation curve, small changes in ventilation, inspired oxygen, and shunt fraction produce large changes in arterial oxygen saturation.

Cardiovascular Response and Limitations during Profound Hypoxemia

Hypoxemia is well tolerated when compensated by cardiovascular responses (fig. 2). Cardiovascular adaptation is the key component of a suite of responses enabling humans to adapt to high altitude hypoxia, endure prolonged breath-hold dives, survive profound acute anemia (hemoglobin less than 5 g/100 ml⁴⁷) and endure other physiologic stressors.³⁰ While biochemical adaptation to hypoxia is also important especially for long term adaptation,^{48,49} cardiovascular adaptation is both the component most strongly coupled to immediate clinical outcomes and the one most easily assessed by clinicians.

The proximal cause of tissue injury in profound hypoxemia is failure of cardiovascular compensation, not hypoxia *per se*. A study in cats⁵ illustrates the critical importance of the circulation in predicting tissue injury during severe hypoxemia: when animals were experimentally exposed to 25 min of severe hypoxia ($FIO_2 = 3.4\%$; $PAO_2 = 17$ mmHg) with adequate blood pressure (mean arterial blood pressure greater than 65 mmHg) not one animal suffered any end-organ injury. In contrast, 12 of 13 cats exposed to the same degree of hypoxemia but with reductions in mean arterial pressure to less than 45 mmHg for only 4 min developed a pattern of brain injury closely resembling that of humans surviving in a persistent vegetative state after cardiorespiratory arrest. Similarly, brain injury in hypoxemic primates only occurs when hypoxia causes low cardiac output.⁶

Cardiovascular compensation underlies the preservation of cognitive function in well compensated profound hypoxemia. Cerebral blood flow increases during hypoxia, preserving cerebral oxygenation out of proportion to systemic hypoxemia⁵⁰ and leaving most cognitive domains little effected by hypoxia.⁵¹ Other studies⁵² have reported intact executive and motor function and mild deficits in memory.

It is of critical importance for clinicians caring for COVID-19 patients to understand that, just as for respiratory system adaptation, cardiovascular compensatory responses are both variable⁵³ and limited. The limits of cardiovascular

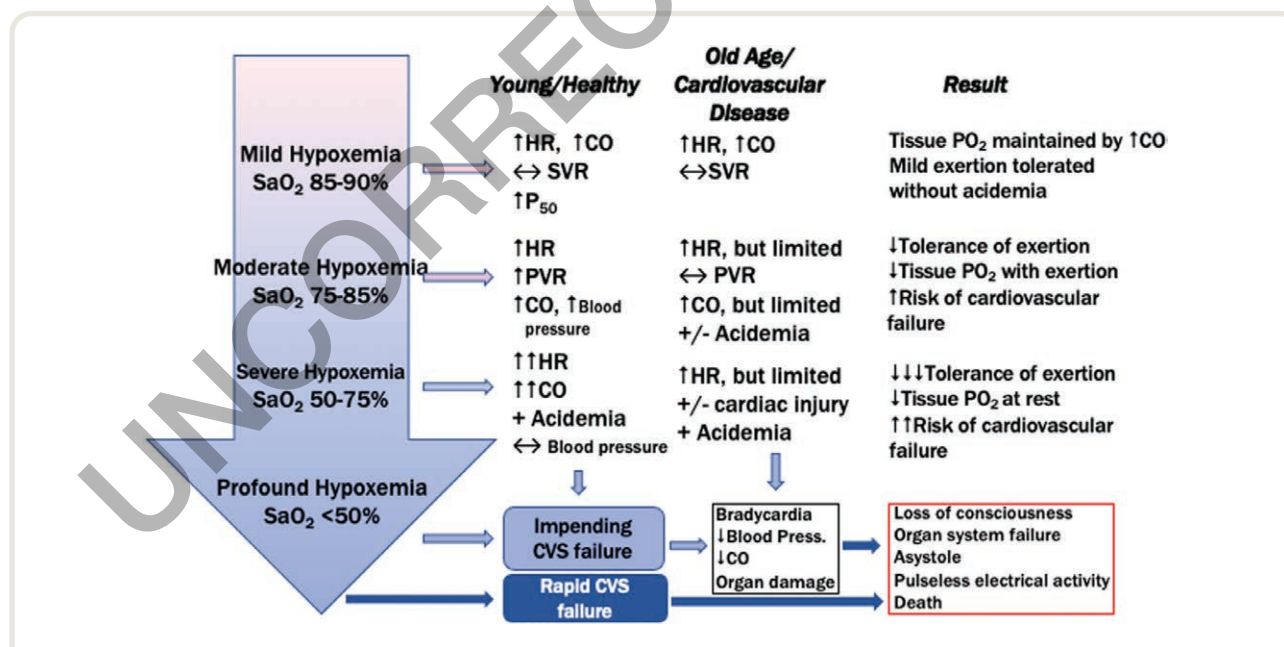


Fig. 2. Cardiovascular compensation for mild (85 to 90% SaO₂), moderate (75 to 85% SaO₂), severe (50 to 75% SaO₂), and profound (<50% SaO₂) hypoxemia. Increased cardiac output, mainly mediated by increased heart rate, is the main cardiovascular response to hypoxemia, but is limited by age and cardiovascular disease. Mild to moderate hypoxemia causes increased cellular glycolysis, which generates 2,3 diphosphoglycerate and increases the P₅₀ of hemoglobin. Decreased tolerance of physical exertion or even normal activity is a sensitive indicator of the adequacy of early cardiovascular response to hypoxemia. Loss of consciousness becomes likely at saturations less than 50%. Failure of cardiovascular adaptation ultimately involves bradycardia, asystole, or pulseless electrical activity, with rapidly ensuing tissue injury and death. CO, cardiac output; HR, heart rate; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

compensation define increasing acidosis and impending cardiovascular collapse and death, as shown in figure 2.

Normal compensated cardiovascular adaptation to acute hypoxemia involves increased cardiac output, mediated predominantly by tachycardia, with only moderate augmentation of blood pressure. As with the breathing response to hypoxemia, this heart rate and blood pressure response to hypoxia vary enormously in healthy individuals.⁵³ The heart rate response to hypoxemia parallels the ventilatory response, so that individuals who do not present with shortness of breath, may also present without significant tachycardia.⁵⁴

Cardiovascular compensation to hypoxemia also varies with age and coexisting disease. We expect that most younger patients with profound hypoxemia have normal or elevated cardiac output, which is one of the most important factors for tolerating hypoxemia. Aging is known to decrease sympathetic nervous system/cardiovascular responses to hypoxic stress, and thereby contribute to a decreased tolerance of hypoxia in older individuals.^{38,39,55} The highest mortality rate in COVID-19 has been reported among older patients¹² who may be less capable of adequate cardiovascular compensation. Individuals with coexisting cardiovascular or pulmonary disease may be limited in the scope or tolerance of sympathetic nervous system activation by systemic hypoxia,⁵⁶ resulting in elevated heart rate, and increases in pulmonary and systemic vascular resistance.

Deterioration in oxygen saturation and cardiovascular compensation can occur rapidly in hypoxemic patients, particularly in patients with profound shunt physiology. It is important to realize that deterioration in oxygenation most often is caused by a combination of factors. These factors include increasing shunt, reduced cardiac output, decreased ventilation (see above), and gas exchange on the steep portion of the oxyhemoglobin dissociation curve. Low cardiac output also worsens pulmonary gas exchange because of decreased mixed venous P_{O_2} ,⁵⁷ right shift of the oxyhemoglobin dissociation curve caused by acidosis, and decreased effectiveness of hypoxic/hypercapnic pulmonary vasoconstriction. In the presence of a fixed intrapulmonary shunt, a lower mixed-venous P_{O_2} will have a large effect on arterial saturation because of the shape of the oxyhemoglobin dissociation curve⁵⁸ (fig. 1). Because alveolar gas exchange is on the steep portion of the oxyhemoglobin dissociation curve, small changes in cardiac output or alveolar P_{O_2} result in large changes in oxygen saturation via this decrease in mixed venous P_{O_2} . Taken together, these effects explain the seemingly unpredictable precipitous changes in oxygenation that can occur in all severe pneumonias.

Predicting the Limits of Cardiovascular Compensation in Profound Hypoxemia

The precise limits of tolerance of reduced oxygen delivery are difficult to predict in an individual patient, but a critical threshold is when oxygen delivery is reduced to less than 25% of normal.⁵⁹ The clinical assessment of the

transition from compensated to poorly compensated cardiovascular adaptation to hypoxemia includes the following: (1) worsened acidemia or plasma lactate^{60,61}; (2) decreased mixed venous P_{O_2} or decreased tissue oximetry (near infrared spectroscopy); (3) increased requirements for vasoactive medications to support blood pressure despite adequate fluid resuscitation; (4) increase in blood pressure reactivity to changes in body position, e.g., not tolerating prone or head-up positions; (5) bradycardia, arrhythmias, EKG changes concerning for ischemia, and increased in heart rate variability; and (6) increased troponin levels or ultrasound evidence of decreased myocardial contractility. These assessments reflect a focus on the cardiovascular compensation/tissue oxygen delivery for hypoxemia rather than on the degree of hypoxemia or hypercarbia *per se*. Bradycardia and decreased cardiac output/myocardial function are described in severe cases of hypoxemic respiratory failure, including COVID-19 disease, and often represent premorbid events.⁶² Given reports of acute cardiomyopathy among patients with COVID-19,^{62,63} clinicians must be keenly aware that the changes listed above may also reflect development or progression of myocardial injury; similarly, patients with low ejection fraction may have significantly less ability to augment cardiac output to compensate for any degree of hypoxemia.

Conclusions

COVID-19 is bringing large numbers of severely hypoxemic patients to medical care and highlighting a known phenomenon of "silent hypoxia." The variability in human breathing response to hypoxemia, as well as the preponderance of shunt physiology early in the course of COVID pneumonia, likely explains lack of dyspnea in some hypoxemic COVID-19 patients. Cardiovascular compensation to hypoxemia is critical for preservation of tissue oxygen delivery. The limits of cardiovascular compensation to hypoxemia are more likely to define clinical outcomes in COVID-19 than is the degree of hypoxemia *per se*.

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Competing Interests

The authors declare no competing interests.

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