Why COVID-19 Silent Hypoxemia is Baffling to Physicians

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Abstract

Patients with COVID-19 are described as exhibiting oxygen levels incompatible with life without dyspnea. The pairing—dubbed happy hypoxia, but more precisely termed silent hypoxemia—is especially bewildering to physicians and is considered as defying basic biology. This combination has attracted extensive coverage in media but has not been discussed in medical journals. It is possible that coronavirus has an idiosyncratic action on receptors involved in chemosensitivity to oxygen, but well-established pathophysiological mechanisms can account for most, if not all, cases of silent hypoxemia. These mechanisms include how dyspnea and the respiratory centers respond to low levels of oxygen, how prevailing carbon dioxide tensions ($PaCO_2$) blunt the brain's response to hypoxia, effects of disease and age on control of breathing, inaccuracy of pulse oximetry at low oxygen saturations, and temperature-induced shifts in the oxygen dissociation curve. Without knowledge of these mechanisms, physicians caring for hypoxemic patients free of dyspnea are operating in the dark—placing vulnerable COVID-19 patients at considerable risk. In conclusion, features about COVID-19 that physicians find baffling become less strange when viewed in the light of long-established principles of respiratory physiology; an understanding of these mechanisms will enhance patient care if the much-anticipated second wave emerges.

Abstract Words=199 words

Case Report Vignettes

MD, 64-year-old man, tested positive for SARS-CoV-2 and was diagnosed with COVID-19. While receiving 6 liters/min oxygen by nasal cannula, pulse oximetry saturation (SpO_2) was 68% and arterial blood gas revealed oxygen tension (PaO_2) 37 mmHg, carbon dioxide tension ($PaCO_2$) 41 mmHg, and arterial oxygen saturation (SaO_2) 75%. Upon questioning, he consistently denied any difficulty with breathing. On examination, he was comfortable, not using accessory muscles of respiration. Comorbidities included diabetes mellitus, hypertension, coronary artery disease and bypass surgery, left carotid endarterectomy, and renal transplantation.

RM, 74-year-old man, tested positive for SARS-CoV-2 and was diagnosed with COVID-19. While receiving 15 liters/min oxygen by reservoir mask, SpO_2 was 62% and arterial blood gas revealed PaO_2 36 mmHg, $PaCO_2$ 34 mmHg, and SaO_2 69%. Upon questioning, he consistently denied any difficulty with breathing (including while drinking). On examination, he was comfortable and not using accessory muscles of respiration. He did not have any comorbidity

EF, 58-year-old man, tested positive for SARS-CoV-2 and was diagnosed with COVID-19. While receiving high-flow nasal cannula, SpO_2 was 76% and arterial blood gas revealed PaO_2 45 mmHg, $PaCO_2$ 38 mmHg, and SaO_2 83%. Upon questioning, he consistently denied any difficulty with breathing. On examination he was comfortable, using his cell phone. He had no known comorbidities.

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The Wall Street Journal considers it a medical mystery as to why "large numbers of Covid-19 patients arrive at hospitals with blood-oxygen levels so low they should be unconscious or on the verge of organ failure. Instead they are awake, talking—not struggling to breathe" (1). *Science* judges the lack of patient discomfort at extraordinarily low blood-oxygen levels as defying basic biology (2). Writing in *The New York Times*, Dr. Levitan, with 30 years of emergency medicine experience, notes "A vast majority of Covid pneumonia patients I met had remarkably low oxygen saturations at triage—seemingly incompatible with life—but they were using their cellphones…they had relatively minimal apparent distress, despite dangerously low oxygen levels" (3). Despite this extensive coverage in the news media, the topic has not been addressed in medical journals.

Several factors explain why oxygen readings and lack of dyspnea in COVID-19 patients are baffling to physicians: effect of hypoxia on the respiratory centers, effect of $PaCO_2$ on the ventilatory response to hypoxia, hypoxia threshold that precipitates dyspnea, limited accuracy of SpO_2 below 80%, shifts in the oxygen-dissociation curve, tolerance of low oxygen levels, and the definition of hypoxemia.

Dyspnea and control of breathing

Viral infection of the respiratory system typically provokes inflammation and stimulation of sensory receptors, inducing transmission of afferent impulses to the respiratory centers (4). If the virus involves the alveoli, it may produce hypoxemia (5). The presence of dyspnea would be no physiological surprise in either situation. Surprise would arise only if sensory afferents or hypoxemia elicited significant stimulation of the respiratory centers and the patient did not develop dyspnea (6).

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Unpleasant breathing can be recognized only by a patient: it is purely a subjective symptom (6). Caregivers commonly equate physical signs—tachypnea, tachycardia, facial expression—with dyspnea. This is wrong. Patients vary widely in behavioral responses to discomfort. As with pain, physical signs may overestimate or underestimate patient discomfort (7).

The respiratory centers are exquisitely sensitive to CO_2 (7). Small increases in $PaCO_2$ rapidly evoke large increases in minute ventilation; an increase in $PaCO_2$ of 10 mmHg produces a level of respiratory discomfort that cannot be tolerated for even a few minutes (8). Abnormal lung mechanics also provokes dyspnea, but considerably less than with hypercapnia (7).

Hypoxemia produces dyspnea through stimulation of the carotid bodies, which send signals to the medulla oblongata (9). The resulting increase in respiratory center output is transmitted down to the phrenic nerves and diaphragm causing increased minute ventilation (10). Heightened medullary center activity is concurrently transmitted up to the cerebral cortex. It is this cortical projection (corollary discharge) that produces the unpleasant sensation of dyspnea (7).

The ventilatory response to hypoxia is characterized as a hyperbolic curve (11). Minute ventilation is unchanged as PaO_2 drops from 90 to 60 mmHg; further decreases in PaO_2 provoke an exponential increase in minute ventilation **(Figure 1)**. Moosavi et al (12) observed that the level of hypoxia required to induce the ventilatory response to hypoxia is equivalent to that required to induce dyspnea. A fall in end-tidal PO_2 below 60 mmHg elicited a strong increase in dyspnea in only half of subjects (12). The ventilatory and dyspnea responses to hypoxia are heavily influenced by prevailing $PaCO_2$. Severe hypoxia elicits an effective increase in ventilation only when background $PaCO_2$ exceeds 39 mmHg (12, 13).

We undertook an informal poll of 58 hospitalists, emergency physicians, and intensivists, inquiring if they had seen patients who might be regarded as having silent hypoxemia or "happy hypoxia" (the term used by newspapers). Of 37 respondents, 15 did not provide useful data. Nineteen patients had arterial blood gases; 16 had PaO_2 less than 60 mmHg and the patient communicated to a physician that he or she was not experiencing difficulty with breathing. Seven of the 16 patients had $PaCO_2$ levels above 39 mmHg (range, 41-49), which combined with PaO_2 of less than 60 mmHg would be expected to induce dyspnea; we considered these patients to have probable silent hypoxemia (see above vignette for patient MD). Nine patients had $PaCO_2$ levels below 39 mmHg (range, 29-37), which can blunt the respiratory centers; we do not categorize these patients as silent hypoxemia (see patient RM and EF vignettes).

A disproportionate number of COVID-19 patients are elderly and diabetic (14). Both factors blunt the response of the respiratory control system to hypoxia. The ventilatory response to hypoxia is decreased by 50% in people older than 65 years (15, 16). Given that dyspnea response to hypoxia parallels the ventilatory response (12), it is likely that older COVID-19 patients are more prone to silent hypoxemia. All but two of our 7 patients with probable silent hypoxemia were 64 years or older (age range 59 to 85 years). The ventilatory response to hypoxia is decreased by more than 50% in diabetes (17, 18). Diabetics also have a 1.8-fold impaired ability to perceive respiratory sensations (19). A further confounding factor is the broad range in respiratory drive between individuals (20). Chemical drive to breathe (in response to hypercapnia and hypoxia) exhibits as much as 300% to 600% variation between one subject and the next (20-23). This wide variability in respiratory drive is another factor that explains why some hypoxic patients do not develop dyspnea.

Hypoxemia as a threat to life

Physicians are fearful of hypoxemia, and many view saturations in the 80s as life threatening. We served as volunteers in an experiment probing the effect of hypoxemia on breathing pattern; our pulse oximeter displayed SpO_2 of 80% for over an hour and we were not able to sense differences between SpO_2 of 80% versus 90% (24). In investigations on control of breathing and oximeter accuracy, subjects experience SpO_2 of 75% (12), or briefly 45% (25), without serious harm. Tourists on drives to the top of Mount Evans near Denver experience oxygen saturations of 65% for prolonged periods; many are comfortable while some sense dyspnea (25).

Pulse oximetry

Pulse oximetry estimates arterial oxygen saturation by illuminating the skin and measuring changes in light absorption of oxyhemoglobin and reduced hemoglobin (26). Oximetry estimated saturation (SpO_2) can differ from true arterial oxygen saturation (SaO_2, measured with a CO-oximeter) by as much as ±4% (5). Oximetry is considerably less accurate at SaO_2 below 80%, partly because of the challenge in obtaining human calibration data (and guarding of information through trade secrets and patent protection). SpO_2 underestimated true SaO_2 by 7% in all three patients in the above vignettes. In subjects exposed to profound hypoxemia in a hypobaric chamber, resulting in arterial oxygen tension (PaO_2) of 21.6–27.8 mmHg (27). the mean difference and limits of agreement between pulse oximetry SpO_2 and true SaO_2 were -5.8±16%; when SpO_2 displayed <40%, 80% of simultaneous SaO_2 values were 10% higher (some were 30% higher)(28) **(Figure 2)**.

Pulse oximetry is less reliable in critically ill patients than in healthy volunteers. In critically ill patients, the 95% limits of agreement between SpO_2 and SaO_2 was $\pm$ 4.02%, and the difference between SpO_2 and SaO_2 over time was not reproducible (in magnitude or direction) (29). Oximetry is less accurate in black than in white patients: 2.45 times less accurate at detecting ≥4% difference between SpO_2 and SaO_2 (30). Claims that COVID-19 patients had oxygenation levels incompatible with life may have arisen because caregivers are not aware that pulse oximeters are inherently inaccurate at low saturations and further impacted by critical illness and skin pigmentation.

Shifts in oxygen-dissociation curve

A shift in the oxygen-dissociation curve is another confounding factor. Fever, prominent with COVID-19, causes the curve to shift to the right; any given PaO_2 will be associated with a lower SaO_2 **(Figure 3)**. At temperature 37°C, PaO_2 60 mmHg (at normal pH and $PaCO_2$) will be accompanied by SaO_2 91.1%. Temperature elevation to 40°C will produce SaO_2 85.8% (5.3% decrease) (31). Respective numbers at PaO_2 40 mmHg are SaO_2 74.1% at temperature 37°C and SaO_2 64.2% at temperature 40°C (9.9% decrease) (31). These shifts produce substantial desaturations without change in chemoreceptor stimulation (because carotid bodies respond only to PaO_2, and not SaO_2) (9)—another factor contributing to silent hypoxemia.

Mechanism of silent hypoxemia

Given that COVID-19 patients exhibit several unusual findings, it is possible the virus has an idiosyncratic effect on the respiratory control system.

Angiotensin-converting enzyme 2 (ACE2), the cell receptor of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the virus responsible for COVID-19, is expressed in the carotid body, the site at which chemoreceptors sense oxygen (32). ACE2 receptors are also expressed in nasal mucosa. Anosmia-hyposmia occurs in two-thirds of COVID-19 patients (33) and the olfactory bulb provides ~~a~~ passage along which certain coronaviruses enter the brain (34). Whether SARS-CoV-2 gains access to the brain through the olfactory bulb and contributes to the association between anosmia-hyposmia and dyspnea (33) and whether ACE2 receptors play a role in the depressed dyspnea response in COVID-19 remains to be determined.

Science (2) links silent hypoxemia to the development of thrombi within the pulmonary vasculature. Increased thrombogenesis has been noted in COVID-19 patients (35). Thrombi within the pulmonary vasculature can cause severe hypoxemia, and dyspnea is related to pulmonary vascular obstruction and its consequences (36). Dyspnea can also arise from release of histamine or stimulation of J-receptors within the pulmonary vasculature. No biological mechanism exists, however, whereby thrombi in the pulmonary vasculature cause blunting of dyspnea (producing silent hypoxemia).

Definition of hypoxemia

Stedman's Medical Dictionary defines hypoxemia as “subnormal oxygenation of arterial blood, short of anoxia” (37). Clinicians, however, need to be mindful of the inverse relationship between PaO_2 and age; a PaO2 of 66 mmHg can be normal in a 80-year old person (38, 39). In the 1990s, hypoxemia was commonly viewed as low PaO_2, and fractional inspired oxygen concentration (F_IO_2) was excluded from consideration (40, 41). Pierson, for example, specified that a mechanically ventilated patient with acute respiratory distress syndrome receiving 100% oxygen and PaO_2 80 mmHg should not be labelled hypoxemic (42).

There is, of course, no pure essentialist definition of hypoxemia—merely a usage (40). To arrive at a present-day nominalist definition of hypoxemia, it appears that few physicians view hypoxemia in the same manner as Pierson. In our informal poll of physicians caring for COVID-19 patients, we specified “I am NOT looking for oxygen requirements, like the number of liters being delivered.” Yet 77.3% of the respondents provided considerable detail on the level of supplemental oxygen, and 36.4% viewed SpO_2 of 90% or higher as compatible with hypoxemia. Although more detailed investigation is necessary, it appears that physicians today commonly define hypoxemia in terms of the amount of oxygen being supplied to a patient.

Judging severity of hypoxemia on the basis of supplemental oxygen is inherently problematic because F_IO_2 is impossible to estimate unless a patient is intubated or breathing room air. With a nasal cannula at 2 L/minute, F_IO_2 ranges anywhere between 24% and 35% (43). To minimize risk of hypoxemia, physicians frequently prescribe oxygen at a level far exceeding physiological needs. Given the flatness of the upper oxygen-dissociation curve, a pulse oximetry reading of 95% can signify PaO_2 anywhere between 60 and 200 mmHg (26, 44)—values that signify markedly different levels of gas-exchange impairment, especially in a patient receiving a high F_IO_2.

Given that hypoxemia is at the very heart of the most severe cases of COVID-19, one wonders if the lack of a widely accepted definition of hypoxemia contributes to some of the confusion and counterclaims associated with the disease.

In conclusion COVID-19 has engendered many surprises, but features that baffle physicians are less strange when contemplated through the lens of long-established principles of respiratory physiology (45).

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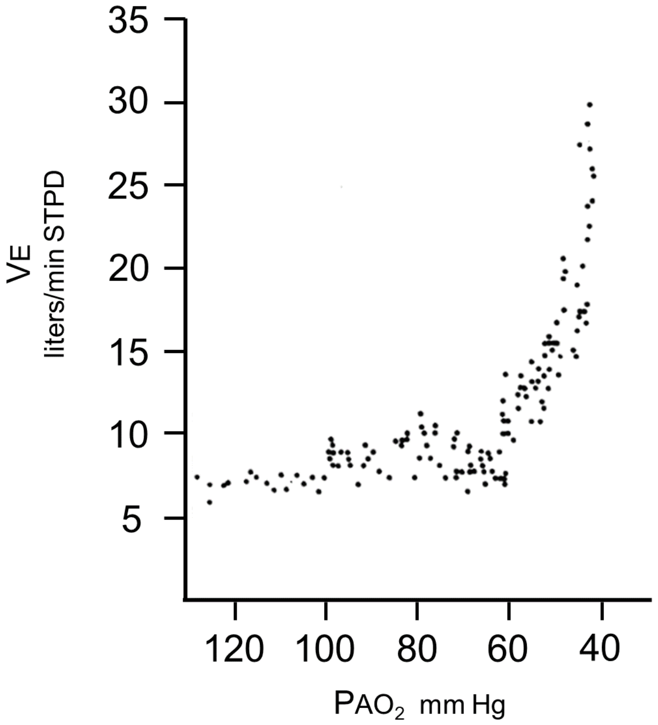

Figure 1. The ventilatory response to progressive isocapnic hypoxia in a healthy subject. Little change in minute ventilation (V_E) is noted until alveolar oxygen tension (P_AO_2) falls to 60 mmHg, and thereafter the response is very steep. Each data point represents the mean value for P_AO_2 and V_E for three successive breaths. From Weil et al (11), with permission. Figure 1.

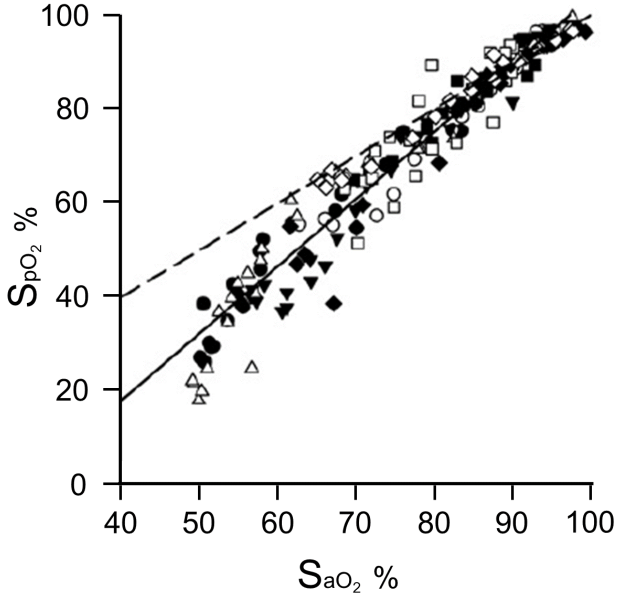

Figure 2 Scatterplot of the relationship between estimated oxygen saturation from pulse oximetry (S_PO_2) and arterial oxygen saturation from blood gas analysis (SaO_2) in healthy subjects exposed to profound hypoxemia in a hypobaric chamber (arterial oxygen tension PaO_2, 21.6–27.8 mmHg). Each subject is represented by a different symbol. The dashed line is the line of identity and the solid line is the regression line. From Ottestad et al (28), with permission.

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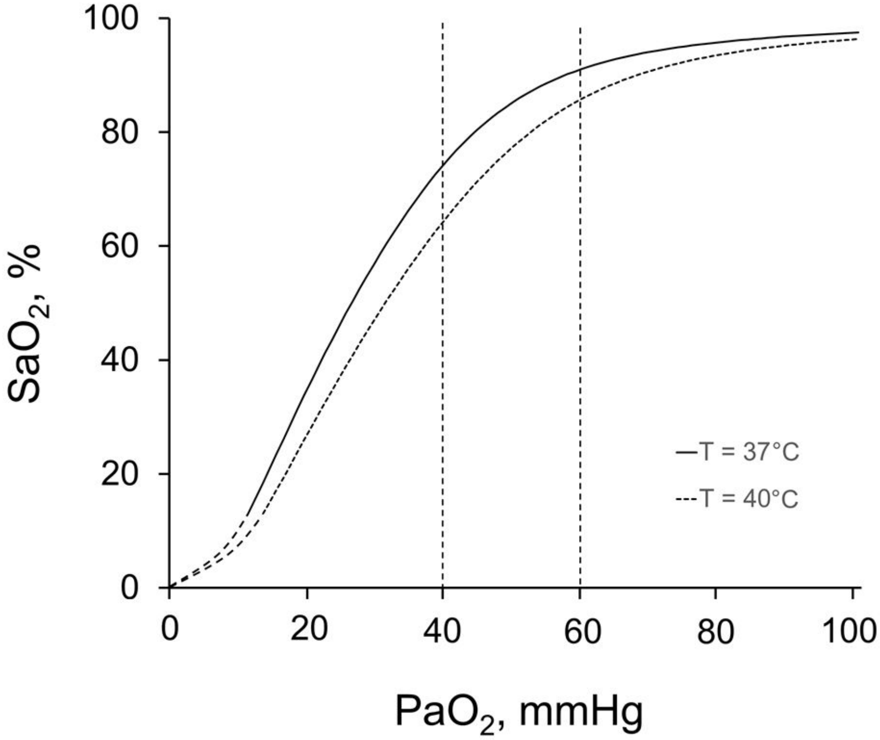

Figure 3 Relationship between arterial oxygen tension (PaO_2) and percentage saturation of hemoglobin with oxygen (SaO_2) at temperature 37°C (continuous line) and 40°C (dotted line), with constant pH 7.40 and PCO_2 40 mmHg (generated with digital subroutine of Kelman (31)). At PaO_2 60 mmHg, SaO_2 is 91.1% at 37°C and decreases to 85.8% at 40°C. At PaO_2 40 mmHg, SaO_2 is 74.1% at 37°C and decreases to 64.2% at 40°C.

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