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CRITICAL CARE PERSPECTIVE

Why COVID-19 Silent Hypoxemia Is Baffling to Physicians

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Abstract

Patients with coronavirus disease (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 the way dyspnea and the respiratory centers respond to low levels of oxygen, the way the prevailing carbon dioxide tension (Pa_{CO_2}) blunts 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 patients with hypoxemia free of dyspnea are operating in the dark, placing vulnerable patients with COVID-19 at considerable risk. In conclusion, features of COVID-19 that physicians find baffling become less strange when viewed in light of long-established principles of respiratory physiology; an understanding of these mechanisms will enhance patient care if the much-anticipated second wave emerges.

Keywords: COVID-19; control of breathing; dyspnea; hypoxemia; pulse oximetry

Case Report Vignettes

Patient MD, a 64-year-old man, tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and coronavirus disease (COVID-19) was diagnosed. While the patient was receiving 6 L/min oxygen by nasal cannula, his oxygen saturation as measured by pulse oximetry (Sp_{O_2}) was 68%, and arterial blood gas revealed oxygen tension (Pa_{O_2}) of 37 mm Hg, carbon dioxide tension (Pa_{CO_2}) of 41 mm Hg, and oxygen saturation (Sa_{O_2}) of 75%. On questioning, he consistently denied any difficulty with breathing. On examination, he was comfortable and not using accessory muscles of respiration. Comorbidities included diabetes mellitus, hypertension, coronary artery disease and bypass surgery, left carotid endarterectomy, and renal transplantation.

Patient RM, a 74-year-old man, tested positive for SARS-CoV-2, and COVID-19 was diagnosed. While he was receiving 15 L/min oxygen by reservoir mask, his Sp_{O_2} was 62%, and arterial blood gas revealed a Pa_{O_2} of 36 mm Hg, a Pa_{CO_2} of 34 mm Hg, and an Sa_{O_2} of 69%. On 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 comorbidities.

Patient EF, a 58-year-old man, tested positive for SARS-CoV-2, and COVID-19 was diagnosed. While receiving a high-flow nasal cannula, his Sp_{O_2} was 76%, and arterial blood gas revealed a Pa_{O_2} of 45 mm Hg, a Pa_{CO_2} of 38 mm Hg, and an Sa_{O_2} of 83%. On questioning, he consistently denied any difficulty with breathing. On examination, he was comfortable and using his cell phone. He had no known comorbidities.

Background

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

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the lack of patient discomfort at extraordinarily low blood-oxygen concentrations 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 patients with COVID-19 are baffling to physicians, including the effect of hypoxia on the respiratory centers, the effect of Pa_{CO_2} on the ventilatory response to hypoxia, the hypoxia threshold that precipitates dyspnea, the limited accuracy of Sp_{O_2} below 80%, shifts in the oxygen dissociation curve, the 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).

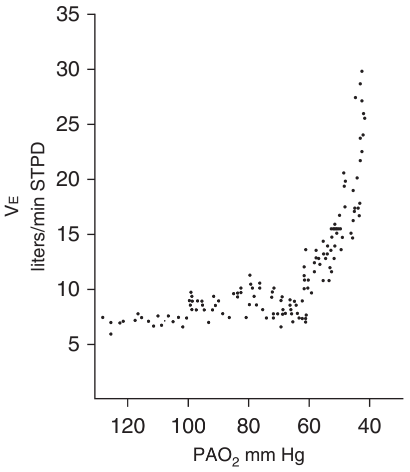

Figure 1. The ventilatory response to progressive isocapnic hypoxia in a healthy subject. Little change in $\dot{V}_E$ is noted until alveolar oxygen tension (PA_{O_2}) falls to 60 mm Hg, and thereafter the response is very steep. Each data point represents the mean value for PA_{O_2} and $\dot{V}_E$ for three successive breaths. Adapted by permission from Reference 11. STPD = standard temperature and pressure dry.

Unpleasant breathing can be recognized only by a patient; it is purely a subjective symptom (6). Caregivers commonly equate physical signs—tachypnea, tachycardia, and 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 Pa_{CO_2} rapidly evoke large increases in minute ventilation ($\dot{V}_E$); an increase in Pa_{CO_2} of 10 mm Hg produces an amount of respiratory discomfort that cannot be tolerated for even a few minutes (8). Abnormal lung mechanics also provoke dyspnea but considerably less than hypercapnia does (7).

Hypoxemia produces dyspnea through the 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 $\dot{V}_E$ (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). $\dot{V}_E$ is unchanged as Pa_{O_2} drops from 90 to 60 mm Hg; further decreases in Pa_{O_2} provoke an exponential increase in $\dot{V}_E$ (Figure 1). Moosavi and colleagues (12) observed that the amount of hypoxia required to induce the ventilatory response to hypoxia is equivalent to that required to induce dyspnea. A fall in end-tidal P_{O_2} to less than 60 mm Hg elicited a strong increase in dyspnea in only half of subjects (12). The ventilatory and dyspnea responses to hypoxia are heavily influenced by the prevailing Pa_{CO_2}. Severe hypoxia elicits an effective increase in ventilation only when background Pa_{CO_2} exceeds 39 mm Hg (12, 13).

We undertook an informal poll of 58 hospitalists, emergency physicians, and intensivists, inquiring whether 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 gas measurements; of these, 16 patients had a Pa_{O_2} of less than 60 mm Hg and communicated to a physician that they were not experiencing difficulty with breathing. Seven of the 16 patients had Pa_{CO_2} concentrations above 39 mm Hg (range, 41–49), which, combined with Pa_{O_2} of less than 60 mm Hg, would be expected to induce dyspnea; we considered these patients to have probable silent hypoxemia (*see* above vignette for patient MD). Nine patients had Pa_{CO_2} concentrations below 39 mm Hg (range, 29–37), which can blunt the respiratory centers; we do not categorize these patients as having silent hypoxemia (see patient RM and EF vignettes).

A disproportionate number of patients with COVID-19 are elderly and have diabetes (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 the dyspnea response to hypoxia parallels the ventilatory response (12), it is likely that older patients with COVID-19 are more prone to silent hypoxemia. All but two of our seven patients with probable silent hypoxemia were 64 years or older (age range, 59–85 yr). The ventilatory response to hypoxia is decreased by more than 50% in diabetes (17, 18). Individuals with diabetes 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). The chemical drive to breathe (in response to hypercapnia and hypoxia) exhibits as much as 300–600% variation between one subject and the next (20–23). This wide variability in respiratory drive is another factor that explains why some patients with hypoxia do not develop dyspnea.

Hypoxemia as a Threat to Life

Physicians are fearful of hypoxemia, and many view saturations between 80% and

85% as life threatening. We served as volunteers in an experiment probing the effect of hypoxemia on breathing patterns; our pulse oximeter displayed an Sp_{O_2} of 80% for over an hour, and we were not able to sense differences between an Sp_{O_2} of 80% and an Sp_{O_2} of 90% (24). In investigations on control of breathing and oximeter accuracy, subjects experience an Sp_{O_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, whereas some sense dyspnea (25).

Pulse Oximetry

Pulse oximetry estimates Sa_{O_2} by illuminating the skin and measuring changes in light absorption of oxyhemoglobin and reduced Hb (26). Pulse oximetry–estimated saturation (Sp_{O_2}) can differ from true Sa_{O_2} (measured with a CO-oximeter) by as much as ±4% (5). Pulse oximetry is considerably less accurate at Sa_{O_2} of less than 80%, partly because of the challenge in obtaining human calibration data (and guarding of information through trade secrets and patent protection). Sp_{O_2} underestimated true Sa_{O_2} by 7% in all three patients in the above vignettes. In subjects exposed to profound hypoxemia in a hypobaric chamber, there was a resulting Pa_{O_2} of 21.6–27.8 mm Hg (27). The mean difference and limits of the agreement between pulse oximetry Sp_{O_2} and true Sa_{O_2} were $-5.8 \pm 16\%$; when Sp_{O_2} was displayed as less than 40%, 80% of simultaneous Sa_{O_2} values were 10% higher (some were 30% higher) (28) (Figure 2).

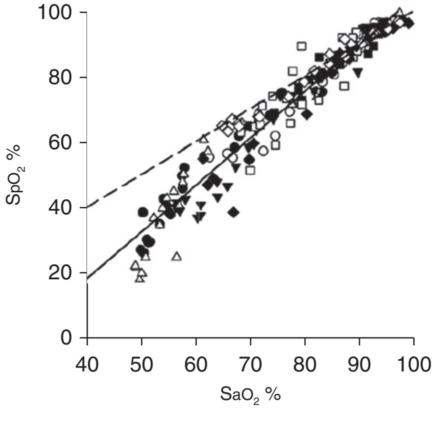

Figure 2. Scatterplot of the relationship between estimated oxygen saturation from pulse oximetry (Sp_{O_2}) and Sa_{O_2} from blood gas analysis in healthy subjects exposed to profound hypoxemia in a hypobaric chamber (Pa_{O_2}, 21.6–27.8 mm Hg). Each subject is represented by a different symbol. The dashed line is the line of identity, and the solid line is the regression line. Adapted by permission from Reference 28.

Pulse oximetry is less reliable in critically ill patients than in healthy volunteers. In critically ill patients, the 95% limit of agreement between Sp_{O_2} and Sa_{O_2} was ±4.02%, and the difference between Sp_{O_2} and Sa_{O_2} over time was not reproducible (in magnitude or direction) (29). Pulse oximetry is less accurate in black than in white patients (2.45 times less accurate at detecting $\geqslant$4% difference between Sp_{O_2} and Sa_{O_2}) (30). Claims that patients with COVID-19 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 Pa_{O_2} will be associated with a lower Sa_{O_2} (Figure 3). At a temperature of 37°C, a Pa_{O_2} of 60 mm Hg (at normal pH and Pa_{CO_2}) will be accompanied by an Sa_{O_2} of 91.1%. Temperature elevation to 40°C will produce an Sa_{O_2} of 85.8% (5.3% decrease) (31). Respective numbers for a Pa_{O_2} of 40 mm Hg are an Sa_{O_2} of 74.1% at a temperature of 37°C and an Sa_{O_2} of 64.2% at a temperature of 40°C (9.9% decrease) (31). These shifts produce substantial desaturations without change in chemoreceptor stimulation (because carotid bodies respond only to Pa_{O_2} and not Sa_{O_2}) (9)—another factor contributing to silent hypoxemia.

Mechanism of Silent Hypoxemia

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

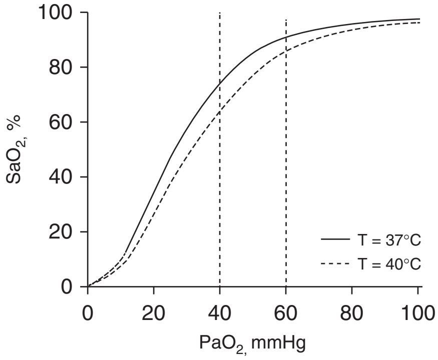

Figure 3. Relationship between arterial oxygen tension (Pa_{O_2}) and percentage saturation of hemoglobin with oxygen (Sa_{O_2}) at temperature 37°C (continuous line) and 40°C (dashed line), with a constant pH 7.40 and P_{CO_2} of 40 mm Hg (generated with digital subroutine of Kelman [31]). At a Pa_{O_2} of 60 mm Hg, Sa_{O_2} is 91.1% at 37°C and decreases to 85.8% at 40°C. At a Pa_{O_2} of 40 mm Hg, Sa_{O_2} is 74.1% at 37°C and decreases to 64.2% at 40°C.

ACE 2 (angiotensin-converting enzyme 2), the cell receptor of 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 patients with COVID-19 (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 remain to be determined.

Science (2) links silent hypoxemia with the development of thrombi within the pulmonary vasculature. Increased thrombogenesis has been noted in patients with COVID-19 (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 the release of histamine or stimulation of juxtacapillary receptors within the pulmonary vasculature. No biological mechanism exists, however, whereby thrombi in the pulmonary vasculature cause blunting of dyspnea (producing silent hypoxemia).