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On Happy Hypoxia and on Sadly Ignored "Acute Vascular Distress Syndrome" in Patients with COVID-19

To the Editor:

We read with great interest the article by Tobin and colleagues (1) on the issue of silent hypoxemia, which is also known as happy hypoxia, and found it to be a nice review of physiologic mechanisms of dyspnea. The authors refer to the definitions and mechanisms of dyspnea in relation to blood gases, pulmonary insults, age, and disease. They also discuss the definitions and effects of hypoxia, the inaccuracies of pulse saturation, and the properties of the oxygen dissociation curve as well as the mechanisms of hypoxemia in patients with coronavirus disease (COVID-19). We agree that all the physiologic concepts recalled by Tobin and colleagues might, in isolation or together, contribute to a blunted ventilatory response to low levels of Pa_{O_2} and to its corollary subjective feeling of normality or the absence of dyspnea. Among these various factors, we do not believe that the poor correlation between oxygen saturation and arterial partial pressure at low levels of saturation can explain happy hypoxia because, as shown in the vignettes of their paper, patients have not only low oxygen saturation as measured by pulse oxymetry (Sp_{O_2}) values but also very low levels of Pa_{O_2} (which, according to Tobin and colleagues' Figure 1, should have led to ventilation levels well above 20 L/min), yet they consistently denied any difficulty with breathing. Similarly, although age and diabetes have a known blunting effect on the ventilatory response to hypoxia, many patients with happy hypoxia are in their 50s or 60s, wherein age effects are not expected to be great, and are not diabetic. Similarly, we would add that if dyspnea is subjective, V_E levels of more than 20 L/min require obvious use of accessory muscles and visible increases in respiratory frequency that patients with happy hypoxia do not show.

We would like to advance that the main reason for the phenomenon of happy hypoxia is the presence of hypocapnia. We have shown several years ago that hypocapnia has such a powerful braking effect on the respiratory center that it can completely abolish any response to repeated exposure to very low Sp_{O2} levels in normal subjects (2). We see no reasons why happy hypoxia should be limited, as Tobin and colleagues claim, to patients without hypocapnia. By the way, hypocapnia and its consequent alkalosis would tend to shift the oxygen dissociation curve to the left, counteracting the rightward shift due to fever.

As to the reasons for hypocapnic hypoxia without dyspnea, there is one that Tobin and colleagues do not mention and that we believe offers the best explanation, as follows: the presence of a right-to-left intrapulmonary shunt (3). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is known to induce vascular proliferation in the lungs demonstrated both in anatomic and radiologic studies (4, 5). We have demonstrated a late right-to-left intrapulmonary shunt by contrast enhanced echocardiography in one patient with COVID-19 without radiologic lung lesions (unpublished observation). This right-to-left shunt will induce hypoxia, leading to a normal increase in ventilation. However, in face of a shunt, hyperventilation will not increase Pa_{O_2} but will certainly decrease Pa_{CO_2}, with CO_2 being more diffusible than O_2. Thus, hypocapnia would develop, abolishing any further increase in ventilation and explaining the absence of enhanced respiratory efforts and, therefore, of dyspnea. This, we contend, is the initial insult of SARS-CoV-2 that has prompted us to coin the acronym "AVDS" for acute vascular distress syndrome (6). When lung lesions become prominent, showing either ground-glass opacities or consolidations, hypoxia could worsen but hypocapnia would lessen, with the consequent normalization of Pa_{CO_2} and the appearance of feelings of difficult breathing.

In conclusion, we believe it is now time to consider the intrapulmonary shunt as the key factor in patients with COVID-19

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that accounts for both the presence of hypoxia and the absence of dyspnea in many of them. ■

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Reply to Jounieaux *et al.*

From the Authors:

We thank Dr. Jounieaux and colleagues for their comments on our Perspective (1).

They raise several points and are especially emphatic about the importance of intrapulmonary shunt in the pathophysiology of coronavirus disease (COVID-19). Observing hypoxemia in a patient with a viral respiratory tract infection—whether associated with florid or feeble infiltrates—is not a surprise. We did not discuss the mechanisms of hypoxemia in our Perspective because one of us had addressed this topic in a recent editorial (2).

The focus of our Perspective was the lack of dyspnea in patients with profound hypoxemia (such as a Pa_{O_2} of 37 mm Hg in our patient M.D.) (1). In their 2002 study, Jounieaux and colleagues (3) reported that a Pa_{CO_2} of between 29.3 mm Hg and 34.1 mm Hg ablated the ventilatory response to hypoxia. In reality, the threshold is higher; response to hypoxia is absent at Pa_{CO_2} of 39 mm Hg (4). Thus, a patient with a Pa_{O_2} of 37 mm Hg (equivalent to an oxygen saturation of 71%) would not be expected to complain of dyspnea if Pa_{CO_2} were 39 mm Hg (or lower) (1).

Jounieaux and colleagues aver that we deem problems with pulse oximetry to be the major explanation for happy hypoxia. We never said that. Physicians recognize that pulse oximetry is remarkably accurate for saturations of 85–100%, but many are not aware that pulse oximetry commonly displays falsely low readings—by 10% or more—at saturations of less than 80% (1). Given that pulse oximetry is the first tool used to evaluate patients with suspected hypoxemia, this inbuilt tendency to exaggerate the severity of hypoxemia is one factor that may have perplexed some physicians evaluating patients with COVID-19. If a pulse oximeter is displaying a low saturation, it is important to obtain an arterial blood gas measurement whenever possible.

In referring to Figure 1 in our Perspective (a plot of the ventilatory response to hypoxia), Jounieaux and colleagues claim that low levels of Pa_{O_2} will induce V_E of >20 L/min. This will happen at a P_{O_2} of ~51 mm Hg in a normocapnic person (1). If Pa_{CO_2} is less than 40 mm Hg, V_E will remain unchanged despite profound hypoxia (4).

Jounieaux and colleagues assert that V_E of >20 L/min instigates accessory muscle recruitment. In a classic study, Campbell demonstrated that sternomastoid activity (during carbon dioxide rebreathing) did not commence until V_E reached 41–105 L/min (5).

COVID-19 has raised many challenges—political, sociological, biological, and clinical—but coinage of a new label (acute vascular distress syndrome) is unlikely to solve these problems. Although intrapulmonary shunt contributes to hypoxia in some patients with COVID-19, shunt does not determine how the respiratory centers respond to hypoxia and whether a patient complains of dyspnea.

Our Perspective was written to provide understanding to physicians (quoted in newspaper articles) who express bewilderment as to the mechanism of happy hypoxia in patients with COVID-19 (1). We listed several likely contributors, including physiological variables that impact operations of the respiratory control system, fever in producing a rightward shift in the oxygen dissociation curve, unreliability of pulse oximetry at saturations below 80%, and varying interpretations (among clinicians) as to what the word hypoxemia means (1).

We are concerned that befuddled or ruffled physicians might take actions that negatively impact patient care, such as inserting an endotracheal tube (for mechanical ventilation) in patients not exhibiting an increase in work of breathing and who display oxygen saturations that are low but far from being a threat to life (1, 6). We are hopeful that clinical decisions based on a scientific understanding of biological processes operating beneath a patient's skin result in more rational care and are less likely to cause harm. ■

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