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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Early Pa_{CO_2} Changes after Initiating Extracorporeal Membrane Oxygenation: Considerations for Future Research

To the Editor:

We read with great interest the article by Cavayas and colleagues in a recent issue of the *Journal* (1). This group demonstrated that early changes in partial Pa_{CO_2} are associated with neurological complications in patients with severe respiratory failure who have undergone extracorporeal membrane oxygenation (ECMO). This great insight could change the current management of ECMO. However, several factors potentially affecting the reported findings should be discussed.

First, there can be a discrepancy between the real maximum change in Pa_{CO_2} during the first 24 hours after initiation of ECMO and the relative change in CO_2, which is calculated by a formula incorporating Pa_{CO_2} before and at 24 hours after initiation of ECMO. The greatest reduction in Pa_{CO_2} can occur immediately after introduction of ECMO. Furthermore, the Pa_{CO_2} immediately before initiating ECMO is not always equivalent to the pre-ECMO Pa_{CO_2} defined in this study because ECMO cannulation involves frequent changes in ventilator settings and body position. Our data on 25 patients who underwent ECMO include a mean of 9 (interquartile range, 6–11) separate arterial blood gas evaluations per patient during the first 24 hours after initiating ECMO, and the lowest Pa_{CO_2} values occurred a median of 6 (interquartile range, 2–13) hours after initiating ECMO (K. Kikutani and colleagues, unpublished results). Using Cavayas and colleagues' (1) definition, the relative change in CO_2 is −23% in our cohort. However, it is doubled to −46% if we use the following formula: (lowest Pa_{CO_2} during the first 24 h after initiating ECMO − maximum Pa_{CO_2} in the 6 h before ECMO introduction)/maximum Pa_{CO_2} in the 6 h before ECMO introduction. Thus, Cavayas and colleagues (1) may have underestimated the real dynamics of Pa_{CO_2} that occur at earlier stages after initiating ECMO.

Second, we consider that there was insufficient consideration of the range of Pa_{CO_2} within which a cerebrovascular response to CO_2 can be preserved. The cerebrovascular response to CO_2 has a linear association with Pa_{CO_2} (2) between certain ranges of Pa_{CO_2}. The lowest cerebral blood flow, corresponding to maximal vascular resistance, appears to occur in the Pa_{CO_2} range of 10–15 mm Hg. Conversely, cerebral blood flow increases by approximately 3–4% for each unit increase in Pa_{CO_2}, reaching its highest degrees when Pa_{CO_2} is 10–20 mm Hg above normal resting values (3). Further changes in Pa_{CO_2} no longer induce vasoconstrictive and vasodilatory reactions, resulting in a sigmoidal correlation (4). Consequently, rapid changes in Pa_{CO_2} do not always induce rapid changes in cerebrovascular tone in patients with severe hypercapnia because cerebrovascular reactivity to Pa_{CO_2} can be absent (3). Subgroup analysis according to the baseline Pa_{CO_2} would be helpful for precise evaluation of the effect of Pa_{CO_2} dynamics.

Finally, common risk factors for neurological complications, including hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, and use of anticoagulants (5), were not included in the multivariate analysis in this study, despite the fact that these risk factors could be potential confounding factors. ■

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