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

Author disclosures are available with the text of this letter at
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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 PaO2 of 37 mm Hg in our
patient M.D.) (1). In their 2002 study, Jounieaux and colleagues (3) reported that a PaCO2 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 PaCO2 of 39 mm Hg
(4). Thus, a patient with a PaCO2 of 37 mm Hg (equivalent to an
oxygen saturation of 71%) would not be expected to complain of
dyspnea if PaCO2 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 PaO2 will induce Ve of >20 L/min. This will
happen at a P02 of ~51 mm Hg in a normocapnic person (1). If
PaCO2 is less than 40 mm Hg, Ve will remain unchanged despite
profound hypoxia (4).

Jounieaux and colleagues assert that Ve 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 Ve 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.
Early PaCO₂ 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 PaCO₂ 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 PaCO₂ during the first 24 hours after initiation of ECMO and the relative change in CO₂, which is calculated by a formula incorporating PaCO₂ before and at 24 hours after initiation of ECMO. The greatest reduction in PaCO₂ can occur immediately after introduction of ECMO. Furthermore, the PaCO₂ immediately before initiating ECMO is not always equivalent to the pre-ECMO PaCO₂ 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 median of 9 (interquartile range, 6–11) separate arterial blood gas evaluations per patient during the first 24 hours after initiating ECMO, and the lowest PaCO₂ 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 CO₂ is −23% in our cohort. However, it is doubled to −46% if we use the following formula: (lowest PaCO₂ during the first 24 h after initiating ECMO − maximum PaCO₂ in the 6 h before ECMO introduction)/maximum PaCO₂ in the 6 h before ECMO introduction. Thus, Cavayas and colleagues (1) may have underestimated the real dynamics of PaCO₂ that occur at earlier stages after initiating ECMO.

Second, we consider that there was insufficient consideration of the range of PaCO₂ within which a cerebrovascular response to CO₂ can be preserved. The cerebrovascular response to CO₂ has a linear association with PaCO₂ (2) between certain ranges of PaCO₂. The lowest cerebral blood flow, corresponding to maximal vascular resistance, appears to occur in the PaCO₂ range of 10–15 mm Hg. Conversely, cerebral blood flow increases by approximately 3–4% for each unit increase in PaCO₂, reaching its highest degrees when PaCO₂ is 10–20 mm Hg above normal resting values (3). Further changes in PaCO₂ no longer induce vasoconstrictive and vasodilatory reactions, resulting in a sigmoidal correlation (4). Consequently, rapid changes in PaCO₂ do not always induce rapid changes in cerebrovascular tone in patients with severe hypercapnia because cerebrovascular reactivity to PaCO₂ can be absent (3). Subgroup analysis according to the baseline PaCO₂ would be helpful for precise evaluation of the effect of PaCO₂ 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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