Nondyspnogenic respiratory failure in patients with COVID-19: another example of myth-building in this new disease?

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TO THE EDITOR: We have read with great interest the paper authored by Barreto-Filho et al. (1), “Nondyspnogenic acute hypoxemic respiratory failure in COVID-19 pneumonia.” Although the notion of blunted respiratory sensation in patients with COVID-19 has already been disputed (2), the authors developed in their viewpoint a physiological case to support the view that SARS-COV virus can decrease the capacity of infected patients to “feel” the effects of their viral pneumonia, leading to “nondyspnogenic hypoxemic respiratory failure.” Based on the evidence and the rationale presented in the paper, we fear that this article may contribute to more “myth-building” around this newly discovered disease. As briefly developed in our letter, the authors are excessively using the “argument from analogy” while making their case, without really bringing evidence of the existence of such a syndrome. They also seem to have disregarded the complex anatomical basis of dyspnea generation, which relies on widespread structures, making an isolated alteration of dyspnea—identical in many of these patients—difficult to conceive, not to mention the common observation of very severe asynchrony in patients with COVID when mechanically ventilated with low tidal volume strategies. Finally, no data obtained from a systematic study of breathing sensations in these patients, against adequate control groups, are presented.

It is intriguing that the authors first acknowledged the fact that isolated acute hypoxemia at the level observed in these patients (who do receive oxygen supplement and typically remain with \( \text{SaO}_2 > 88\% \)) is unlikely to produce significant dyspnea, rendering obsolete the need to discuss the notion of “nondyspnogenesis,” as previously argued by Tobin et al. (2). Perhaps as importantly, unless a patient has underlying lung disease, COVID-19 viral infection does not cause hypercarbia or alteration in respiratory mechanics, during mild forms of multifocal pneumonia, that would be severe enough to produce major breathing sensation, at least at rest. Yet, the authors are trying to describe the possible physiological basis for a nondyspnogenic acute hypoxemic respiratory in COVID-19 pneumonia, an entity that they are not even sure is real.

Equating the capacity of this virus to invade neurons, both experimentally and clinically, with an alteration in dyspnea sensation (1) is certainly a big leap in reasoning. Simply stated, the sensation of dyspnea can be understood as resulting from the collection of peripheral sensing inputs processed centrally in the brainstem, increasing in turn the neural output to the respiratory muscles while sending a “copy” of this information toward the thalamus, the limbic system, and the sensorimotor cortex, where the sensation becomes “conscious” (3–5). Therefore, it would be difficult, if not impossible, to imagine lesions of the central nervous system exclusively affecting breathing sensations to be systematically present in a large proportion of patients with COVID-19 without alteration in any other sensory or motor functions that are processed in the same areas. For instance, the authors reference literature on the role of the vagal and glossopharyngeal nerves in the ventilatory response and breathing discomfort during hypercapnia. True as this may be, it does not address the core argument of why and how COVID-19 should be presenting with a reduced sensation of dyspnea. If cranial nerves were affected, we should expect patients to have deficits in the functions of these nerves that would manifest as changes in gastrointestinal motility, cardiac response, gag reflex, etc. Furthermore, if the virus was to affect deeper brain structures, such as the nucleus of the solitary tract or more extensively the dorsal or ventral medulla, which may indeed affect the responses to hypoxia and respiratory sensations, such lesions would not account for an isolated decrease in shortness of breath. Indeed, when limited and unilateral defects are affecting the rostral medulla, abnormal symptoms ranging from hypoventilation during sleep and reduced \( \text{CO}_2 \) sensitivity to severe respiratory and cardiovascular control abnormalities are present (6, 7), whereas bilateral or more widespread lesions are usually lethal (8). These changes are not reliably observed in patients with COVID-19, who typically do not experience hypercapnia or certainly not severe respiratory and cardiovascular control abnormalities. The same reasoning can be applied to more rostral structure, including the thalamus, the limbic, or the sensory cortex (wherein painful sensations are also encoded) (9). We concede that the generation of dyspnea could be altered in patients with COVID-19 in coma with diffuse encephalitis; however, most patients who present with hypoxemic pneumonia have no neurological symptoms that would be compatible with the diagnosis of diffuse encephalitis.

Finally, most clinicians caring for intubated and mechanically ventilated patients with COVID-19 will have observed striking phenomena of asynchrony. When invasive mecha-
nical support becomes necessary, lung-protective ventilation imposes the use of low tidal volume (LTVV), a mode of ventilation that is typically poorly tolerated in the unsedated patients due to increased drive to breathe and respiratory discomfort. Like many other types of patients on LTVV, patients with COVID “overbreathe” the ventilator, generating tidal volumes much larger than the ventilator is set to deliver, requiring a large amount of sedation (and most of the time the use of paralytic agents), suggesting that their capacity to “sense and respond” to inadequate peripheral signals or centrally mediated information are likely to be intact, if not exaggerated.

In conclusion, convicting proofs supporting the existence of isolated nondyspnogenic respiratory failure in patients with COVID-19 suffering from pneumonia are still lacking, making the search for the physiological basis of this still questionable entity quite challenging.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

J.N. and P.H. drafted manuscript; J.N. and P.H. edited and revised manuscript; J.N. and P.H. approved final version of manuscript.