TO THE EDITOR: We read with great interest the many comments made by Nuschke and Haouzi (1) regarding our manuscript (2). Their main criticism is stated in their letter title claiming we contribute to building a myth in COVID-19.

We agree with several of the pathophysiological arguments highlighted by them, especially when reporting to Tobin’s argument against isolated hypoxemia contributing to dyspnogenesis (3) and that no robust data addressing breathing sensation in COVID-19 were presented.

Despite we have presented these same criticisms addressed by them, we feel they misunderstood and did not capture the proposal of our speculative hypothesis and, moreover, they neglected the potential importance of debating clinical observations with a scientific perspective (4).

COVID-19 is a new disease, and the pieces of this complex puzzle are almost unknown. During pandemic, waiting to have systematic epidemiological data about the proposed peculiar COVID-19 presentation named “silent,” “happy,” or “apathetic” hypoxemia, to then speculating a mechanism, may be too rigid and not very wise (4). As stated, our speculative personal hypothesis was based on several clinical reports around the globe, including our own personal in-field experience, with respect to the apparently lack of dyspnea observed in some patients with COVID-19 presenting and very severe hypoxemic respiratory failure. Moreover, we stressed out that we will need epidemiological studies to confirm this as a peculiar clinical entity of COVID-19. Nevertheless, it is at least very intriguing that “silent hypoxemia” had not been described before COVID-19 outbreak in patients with bacterial or common viral pneumonia. Moreover, that the scientific literature about the prevalence and factors associated with dyspnea sensation, in different clinical scenarios, is practically nonexistent. Although we have data about silent myocardial infarction, severe hypoxemic respiratory failure presenting with blunt dyspnea, as a clinical entity, was just raised during COVID-19 outbreak. Tobin’s pathophysiological arguments are very solid but are not sufficient to disqualify different points of view.

The idea that only “anatomofunctional” topographic brain or nerve lesions may dysregulate dyspnea sensation is misleading. Mounting of evidence has been accumulating that patients with and survivors of COVID-19 can suffer neurological symptoms like “brain fog” and difficulty in concentrating independently of having specific topographic lesions. The patient apathy associated with severe hypoxemic respiratory failure seems to be a distinct and peculiar clinical finding in COVID-19, independently of the patient’s age.

Moreover, in a recent study profiling 65,309 single-nucleus transcriptomes from 30 frontal cortex and choroid plexus samples across control individuals and patients with COVID-19, it was observed broad and profound cellular perturbations, brain inflammation, and microgliosis and astrocyte subpopulations that share features with human neurodegenerative diseases (5). Curiously, these pathological findings were not associated with molecular traces of SARS-CoV-2 in the brain. That patients with severe COVID-19 pneumonia have a peculiar involvement of neurological function and that may blunt dyspnea sensation seems to us a plausible hypothesis and we took the risk to propose a conceptual working hypothesis to address this important scientific question just emerged in COVID-19 outbreak. Time combined with high-quality research will let us know whether our hypothesis is true.

DISCLOSURES

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

AUTHOR CONTRIBUTIONS

J.A.B.-F., J.D.S.-G., F.B.G., T.S.M., and L.F.D. drafted manuscript; J.A.B.-F., J.D.S.-G., F.B.G., T.S.M., and L.F.D. edited and revised manuscript; J.A.B.-F., J.D.S.-G., F.B.G., T.S.M., and L.F.D. approved final version of manuscript.
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