TO THE EDITOR: I read the critiques of Xu et al. (1) relating to our paper (2) and I would like to comment on them further clarifying some aspects of the original work.

The authors state that choosing 10% as a threshold for randomly generated distributions is “approximate at best” and our “methodology for identifying V/Q distributions to describe the patient data was not particularly successful.” I firmly disagree. We simply performed a sort of Monte Carlo simulation trying to identify the common features of the V_A/Q distributions that might be reasonably representative of the real one. As shown in Supplemental Fig. E3 in the original paper (https://doi.org/10.6084/m9.figshare.13061075.v1), the V_A/Q distributions we found all shared, as a common trait, an impressive presence of highly perfused regions. Moreover, we later reasoned that the distance between the high-density region of the point clustering and the true gas point is indirectly linked to the degree of hypoxic vasoconstriction.

The concern about N_2 convective exchange is certainly intriguing. I wonder, however, if allowing for a further degree of freedom in our model had actually led to a better understanding of the underlying physiology of subjects in whom few, retrospectively collected data were available. As a side note, I would also remind the authors that the model used as a conceptual background for our work, in presence of low V_A/Q regions and without diffusion limitation, allows a very accurate prediction of the P_AO_2 of the subjects, without the need to alter the alveolar gas Eq. (3).

Most importantly, the authors state that “we consider it likely that their starting assumption that the shunt blood flow fraction is proportional to the nonaerated lung fraction is incorrect.” On the contrary, it is, but the proportion is likely far from 1:1. Indeed, we stated in the manuscript: “...Therefore, we cannot exclude that, at least in part, what Vent_{Qbar} classified as regions with extremely low V_A/Q may actually represent shunt (V_A/Q = 0)” and “the model is able to provide useful insights into the patient’s gas exchange until the basic assumption that shunt = nonaerated tissue fraction holds true. In the presence of strong hypoxic vasoconstriction or, conversely, loss of it, the link between the two variables is broken.” Indeed, not only the shunt fraction is proportional to the nonaerated lung fraction but it also far exceeds it. It is worth reminding that a proportion between shunt and nonaerated lung tissue fraction of 1:1 is already an overestimation, as it implies a complete absence of hypoxic vasoconstriction. Here lies the fundamental, clinical observation: the hypoxemia observed depends either on a V_A/Q mismatch in the range of the largest ever observed or on the severe overperfusion of consolidations or even on vascular shunts, unrelated to the consolidations. In any case, this is fundamentally different from what happens in acute respiratory distress syndrome of non-COVID-19 etiology (4).

Lastly, the claim of the authors that COVID-19 “…is likely to impair hypoxic pulmonary vasoconstriction and contribute to a shunt fraction significantly greater than otherwise expected” comes as no surprise, as we were the first to hypothesize this, more than 1 year ago (5). This paper further reinforces the concept, with quantitative estimates, that the loss of hypoxic vasoconstriction must be extremely severe and/or further, unconventional mechanisms leading to hypoxemia are at play. Only through proper, quantitative V_A/Q measurements, we will be able to further elucidate the underlying pathophysiology of this disease.

**DISCLOSURES**

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

**AUTHOR CONTRIBUTIONS**

M.B. drafted, edited and revised, and approved final version of manuscript.

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