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CORRESPONDENCE

From phenotypes to black holes… and back

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Dear Editor,

We thank Rajendram et al. [1], who—with an amusing use of a pun—point out a "hole" in our Editorial. This physical and metaphorical hole is clearly the presence of a patent *foramen ovale* (PFO) as an additional mechanism in the hypoxaemia observed in COVID-19. Although PFO is frequently found in the general population [2], we have not documented any cases in which PFO significant enough to (even partly) explain the hypoxaemia. All our patients undergo echocardiography to exclude structural or functional heart abnormalities that may explain or contribute to respiratory failure (e.g. severe mitral regurgitation or, indeed intracardiac shunt). It is clear that if such an abnormality was to be found—the whole idea of phenotypes is no longer relevant is the hypoxaemia may be explained by intracardiac shunt regardless of presence or absence of COVID-19 [2]. This argument is also valid for any ventilated patient. Therefore, we do not share the enthusiasm of Rajendram et al. [1], to further sub-classify phenotypes. We intended to present a conceptual framework that can aid the selection of the ventilatory strategy, while avoiding the use of multiple and confusing acronyms. We however fully agree with Rajendram et al. that echocardiography is an essential tool for the diagnosis and management of all ventilated patients whether with classical or 'atypical' ARDS.

We read with interest the letter by Jain et al. [3], who summarise some of the understanding of the ACE-2-mediated dysregulation of pulmonary perfusion in COVD-19, and delineate an 'epithelial-endothelial cross-talk' as a possible mechanism for hypoxaemia. The mechanism they propose is certainly plausible and consistent with the biology of ACE-2 receptors [4, 5] and with some phases of the history of the disease.

However, despite the undeniable temptation to provide a unified mechanism to explain the dysregulated ventilation/perfusion relationship in COVID-19, the interaction between the heterogenous distribution of the disease, the variable amount of pulmonary oedema, the ventilation strategy received and the duration of symptoms, make the search for a single explanatory mechanism simplistic. In addition, inflammation and thrombosis [6] can lead to occlusion of the vasculature that will increase dead space and contribute to the increase in minute ventilation and work of breathing. We disagree, however with Jain et al. when they state that P-SILI is an unlikely mechanism of the worsening of the respiratory function in COVID-19. Indeed, in many institutions the use (sometimes prolonged) of non-invasive support (NIV or CPAP) is a frequent strategy for managing COVID-19 pneumonitis [7, 8]. It is clear that NIV or CPAP will not lead to P-SILI in all instances. If the support is able to reduce the respiratory effort (trans-pulmonary pressure), and the of the disease follows a more benign course the hypoxaemia will resolve. However, uncontrolled work of breathing can lead to additional oedema and lung injury and can explain some of the results found in the literature that describes the outcomes of patients with hypoxemic respiratory failure who undergo initial treatment with non-invasive strategies [9–11]. These results may be applicable to COVID-19.

We would like once again to stress the difference between having a conceptual pathophysiological framework versus having an explanatory biological model. Our intention was to suggest the former while recognising the difficulties in describing the latter [12, 13]. The model we describe, whilst based on physiological considerations, has a high degree of pragmatism to suit front-line management and triage decisions in the many patients who have fallen victim of COVID-19 pneumonitis.

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Compliance with ethical standards

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