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VIEWPOINT

Should we treat COVID-19 lung injury like ARDS? Exploring the paradigm

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Linked articles: This Viewpoint highlights an article by Cronin *et al*. To read this paper, visit https://doi.org/10.1113/EP089400.

When the first COVID-19 patients were admitted to intensive care units in early 2020, intensivists may have thought they knew how to manage them. After all, they had been in the business of treating adult respiratory distress syndrome (ARDS) or viral pneumonias for the best part of their careers. However, it soon became clear that this new disease was different – it looked like ARDS, but it did not always behave like ARDS. A year and a half later, we have gained considerable clinical experience managing mechanical ventilation in patients with severe COVID-19 lung injury. However, existing guidelines are still largely based on our knowledge of classical ARDS, prior to COVID-19 (WHO, 2021).

In this issue of *Experimental Physiology*, Cronin and colleagues (2022) challenge the paradigm that both conditions should be managed in the same way. The authors show that, in later disease, a more classical ARDS pathophysiology emerges, with poor pulmonary compliance relating to progressive consolidation and, in some cases, fibrosis. However, they also provide evidence from clinical, radiological and postmortem studies that COVID-19 patients often demonstrate a different pattern of lung injury from that seen in classical ARDS. Although similar degrees of hypoxaemia are seen in ARDS and *early* COVID-19, its physiological origin seems different: lung architecture is remarkably different, as is pulmonary compliance (relatively preserved in early COVID-19). Growing evidence suggests that the hypoxaemia of early COVID-19 is attributed to pulmonary macro- and/or micro-thrombi, abnormal neovascularisation and other vascular inflammatory changes. Due to these differences in lung compliance and dead space relative to classical ARDS, the authors suggest that using the driving pressure (<14 cmH_2O) of positive pressure mechanical ventilators, and making regular assessments of lung recruitment, is preferable when choosing the optimal tidal volume and positive end-expiratory pressure compared to the standard approach for ARDS of using a fixed tidal volume (6 ml/kg) (The Intensive Care Society, 2018). In this way, they suggest, it may be possible to avoid further impairment of pulmonary blood flow, hypoventilating compliant lungs and over-distending stiff, non-recruitable lungs. Knowledge of symptom onset, time to intubation, lung mechanics and radiographic changes on computed tomography imaging might help to inform these decisions.

The authors acknowledge that this model does not apply to all COVID-19 patients, and furthermore that a transition and overlap may exist between the hypoxic compliant and non-compliant stages. Given these uncertainties, it may be of value to address the following questions. First, it would be useful to better characterise heterogeneity of ventilation/perfusion in severe hypoxia with compliant lungs (referred to as Type L disease by the authors). Further, what is causing the alteration in vascular response? Diverse and complementary approaches are needed, ranging from animal studies to human imaging studies and assessment of blood flow distribution and responsiveness. 'Deep phenotyping' or 'precision medicine' describes a multilayered model of phenotypic analysis that may include genomic, epigenomic, proteomic, metabolomic and immunomic analysis. With the aid of computational biology it is possible to combine multiple complex factors, to find a potential phenotypic composite (Bos et al., 2021). This methodology may help to produce prognostic biomarkers or provide better reference points for testing treatment strategies in COVID-19 lung injury, which are targeted and patient-specific.

Second, understanding the drivers of Type L progression to low compliance is needed, such that mitigating strategies or novel therapeutic interventions can be defined. For instance, the impact of high respiratory rates and tidal volumes in causing lung injury

early in disease (so-called patient self-inflicted lung injury (P-SILI)) should be explored, as might the role of, and interplay with, vascular abnormalities (including in situ thrombosis) unique to COVID-19 lungs.

Trials are required to demonstrate the value of the approach suggested by the authors.

The authors make clear that one key lesson learned in treating COVID-19 patients might be that there is not a 'one size fits all' ventilatory strategy, and indeed managing patients in this way may cause harm. More than 20 years have passed since the landmark ARDSNet trial (Acute Respiratory Distress Syndrome Network et al., 2000) which has resulted in the largely ubiquitous use of a single strategy for mechanical ventilation. Perhaps COVID-19 has given us the opportunity to pause and re-evaluate how we manage classical ARDS too.

Finally, and perhaps above all, this review makes clear that the study of physiology – whether whole-human, animal model or cellular – is essential if new (and existing) disease states are to be better managed. Clinicians and 'pure physiologists' have much to learn from one another. It is time that they began to once again collaborate.

COMPETING INTERESTS

None declared.

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