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COVID-19-related acute respiratory distress syndrome: lessons learned during the pandemic

In 2020 and 2021, SARS-CoV-2 put enormous pressure on our health-care systems. Countless patients with COVID-19 were admitted to hospitals for oxygen support, or to intensive care units (ICUs) when respiratory failure required a more intensive treatment. This hectic situation did not stop the ICU community from providing excellent care, even though most clinicians working in the early stages of the pandemic struggled with many uncertainties, including how best to provide respiratory support. Meanwhile, the critical care community was able to design and conduct a large volume of clinical studies, to settle, and as we look ahead to further surges of COVID-19 perhaps as much as we had seen in the two preceding decades combined. Now that the dust has started to settle, and as we look ahead to further surges of COVID-19, it is worth considering what lessons we have learnt.

Individualisation of ventilation of patients with acute respiratory distress syndrome (ARDS) attracted much attention just before the COVID-19 pandemic. With the exception of low-tidal-volume ventilation, restrictive fluid management, and prone positioning, the previous two decades of ARDS research had not yielded any effective treatment strategies. A reduction of clinical and biological heterogeneity through the identification of ARDS subphenotypes was recognised as a promising method to move towards a precision medicine approach in research and clinical practice.

Early in the pandemic, it was suggested on the basis of small case series that in a subgroup of patients, the severity of hypoxaemia was disproportional to the reduction in lung volume and decreased mechanics of the respiratory system (ie, respiratory system compliance $C_{rs}$). In contrast to patients who had severe hypoxaemia with a decreased $C_{rs}$ and consolidated lung, which is regarded as the classic combination in conventional ARDS, this subgroup of patients had severe hypoxaemia without major changes to aeration and respiratory system mechanics. If this suggestion proved to be true, it would have major implications for ventilatory management (eg, how to set positive end-expiratory pressure [PEEP]) in this patient subgroup. Despite debate within and criticism from some members of the research and clinical communities, these findings influenced ventilatory management in many patients with COVID-19-related ARDS.

In this issue of The Lancet Respiratory Medicine, Mallikarjuna Ponnapa Reddy and colleagues report the results of a well performed systematic review and meta-analysis of 37 studies of COVID-19-related ARDS published between 2019 and 2022. In 11356 patients, mean reported $C_{rs}$ was 35.8 mL/cm H$_2$O (95% CI 33.9–37.8). Mean reported $C_{rs}$ was normally distributed and inversely related to ARDS severity (39.3 mL/cm H$_2$O [36.6–42.0] in mild ARDS, 34.9 mL/cm H$_2$O [32.8–36.9] in moderate ARDS, and 27.3 mL/cm H$_2$O [23.3–31.2] in severe ARDS). In other words, Reddy and colleagues could not confirm, on the basis of $C_{rs}$, the presence of two different subphenotypes in patients with COVID-19-related ARDS.

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Thus, the findings of this report argue strongly against the use of ventilatory strategies that differ from those used in patients with conventional ARDS.

We concur with Reddy and colleagues’ hypothesis that the apparent presence of two subphenotypes of COVID-19-related ARDS might have resulted from the policy to intubate early (ie, at arrival in the ICU or on ICU admission) in patients with hypoxaemic COVID-19. This policy—which reflected the fact that less invasive respiratory support was scarce, if not unavailable, during the first weeks of the pandemic, and might also have been implemented to minimise the risk of infections in health-care workers—could have created a subgroup of patients with hypoxaemia who exhibited high CRS. These patients could have received less invasive support later in the pandemic, and therefore might have disappeared from the cohorts described in the literature.

We have also searched for subphenotypes of COVID-19-related ARDS. We found no evidence for cross-sectional respiratory subphenotypes using unbiased data analysis. When considering longitudinal trends in measures of respiratory system mechanics or lung function, we identified subphenotypes with a worsening ventilatory ratio and mechanical power of ventilation. Upon external validation, the subphenotype with an upward ventilatory ratio trajectory was consistently associated with worse outcomes. Importantly, CRS did not contribute substantially to the observed heterogeneity in these analyses.

These reported findings lead to one important question: is COVID-19-related ARDS really a new clinical entity? We believe that the ventilatory management of COVID-19-related ARDS should not be approached any differently from that of ARDS related to other causes. In our view, the most important factor driving our appreciation of subphenotypic differences was that we had never seen so many patients with ARDS in such a short period of time, which led us to observe all kinds of patterns in clinical presentation.

The reported findings also raise a practical problem: how should the ventilator be set in patients with COVID-19-related ARDS? Based on the evidence that COVID-19-related ARDS is not an atypical form of ARDS, the simple answer could be that the ventilator should be set in the same way as for conventional, albeit heterogeneous, ARDS related to other causes. The individualisation of ventilation management is receiving increasing attention; for example, in how we set PEEP. In this context, the ART (Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial) study showed reduced overall survival in patients who received an optimal CRS-targeted high-PEEP strategy with recruitment manoeuvres compared with those who received a lower-PEEP strategy without recruitment manoeuvres. This finding was nuanced by a Bayesian analysis in ART, which suggested that a high-PEEP strategy is especially detrimental in patients with ARDS caused by a pneumonia. The LIVE (Lung Imaging for Ventilator Setting in ARDS) study, however, suggested that patients with non-focal ARDS could benefit from high PEEP whereas patients with focal ARDS would not.

Considering that COVID-19-related ARDS could be classified as ARDS caused by a pneumonia, should it then be concluded that a high-PEEP strategy in these patients should be avoided? In line with this proposal, use of lower PEEP in patients with COVID-19 is supported by a 2021 analysis of a large cohort of patients with COVID-19, in which the use of high PEEP was associated with worse outcomes compared with the use of lower PEEP. However, if we consider COVID-19-related ARDS to be mainly a non-focal form of ARDS, and thus recruitable, benefit from higher levels of PEEP might be anticipated. Therefore, the optimal PEEP strategy for patients with COVID-19-related ARDS remains an open question.

The study by Reddy and colleagues has taught us one important, and overall, lesson: we should always take a cautious approach when interpreting small case series, and we should change practice only on the basis of firm evidence.

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Moving the pathway goalposts: COPD as an immune-mediated inflammatory disease

Chronic obstructive pulmonary disease (COPD) encompasses a spectrum of lung disorders that cause lung function decline. The degree by which lung function has decreased is used to classify disease severity and as a guide for escalated long-acting bronchodilator use. This strategy aims to modify symptoms but does not target the inflammatory processes that drive disease progression. COPD has distinct, but non-mutually exclusive, endotypes such as chronic bronchitis and emphysema.1 These endotypes each have unique pathogeneses, and diagnosis of COPD is often not consistent between individuals in terms of immunopathology. Arguably, it is this complex disease pathogenesis and a focus on managing and modifying symptoms rather than targeting specific disease pathways that has led to an under-developed therapeutic pipeline. To improve COPD outcomes, novel therapeutics are desperately needed to halt chronic inflammation and disease progression.

There have been decades of progress relating to the treatment of immune-mediated inflammatory diseases. Disease remission is now a realistic goal, and improvements in patient quality of life have been substantial across several diseases. Included in this group of diseases are a collection of seemingly unrelated clinical entities sharing perturbations of immune and inflammatory responses in multiple target organs—diseases such as asthma, atopic dermatitis, autoimmune neurological diseases, psoriasis, type 1 diabetes, inflammatory bowel diseases, rheumatoid arthritis, psoriatic arthritis, and spondyloarthritis.2 In these diseases, dysregulation of immunity and inflammation is considered central to disease pathogenesis and has fostered a drive to understand, and subsequently modify, immune pathways for novel therapeutic development. A similar approach in COPD has been previously considered at the point of exacerbation, with distinct viral, bacterial, eosinophilic, or pauci-immune inflammatory pathways being described in subsets of patients.3 Here, we propose that considering COPD as an immune-mediated inflammatory disease and immunophenotyping patients could help to identify specific patient immune clusters for biological therapies in ways that have been successful for the conventional immune-mediated inflammatory diseases.

The pathogenesis of COPD is still not fully understood, but chronic activation of epithelial cells and macrophages by noxious inhaled particles has been proposed to initiate development. These cells orchestrate an innate pro-inflammatory environment (including IL-8, monocyte chemoattractant protein-1, and reactive oxygen species) by recruiting polymorphonuclear...