

EDITORIAL



Is severe COVID-19 pneumonia a typical or atypical form of ARDS? And does it matter?

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The coronavirus disease 2019 (COVID-19) pandemic has proven remarkable for many reasons, among them its capacity to provoke controversy and debate. One hotly debated question is whether severe COVID-19 pneumonia should be classified simply as another cause of acute respiratory distress syndrome (ARDS), or as a particular subtype of ARDS with pathophysiological features so unique that a different approach to ventilatory management is needed. Does severe COVID-19 pneumonia fall within the usual pathophysiological spectrum of ARDS or is it a qualitatively different disease state? And what consequences might the answer to this question hold for the optimal ventilatory management of severe COVID-19?

In a recent article, Chiumello et al. approach these questions by comparing the respiratory pathophysiological features of patients with early COVID-19 ARDS to historical controls with classical (non-COVID-19) ARDS [1]. A hallmark of classical ARDS is that hypoxemia results predominantly from atelectasis and consolidation, with a consequent increase in physiological shunt fraction [2, 3]. In the matched cohort study, Chiumello et al. demonstrated exactly this in patients with classical ARDS: both venous admixture and hypoxemia ($\text{PaO}_2/\text{FiO}_2$ ratio) were correlated to the fraction of non-aerated lung. In their patients with COVID-19 pneumonia, by contrast, they found that venous admixture and $\text{PaO}_2/\text{FiO}_2$ were not correlated to the fraction of non-aerated lung, suggesting a different mechanism of hypoxemia. Moreover, the severity of hypoxemia appeared to be out of proportion to the impairment in lung mechanics.

When matched on compliance, patients with COVID-19 ARDS had more severe hypoxemia; and when matched on hypoxemia, they had relatively preserved compliance compared to patients with classical ARDS. The authors concluded that COVID-19 ARDS should be regarded as an “atypical subset of ARDS.”

These conclusions accord with the pathological findings revealing unusual involvement of the pulmonary microvasculature and associated coagulopathy [4, 5]. As Chiumello et al. point out, patients in their COVID-19 ARDS cohort seem to have strikingly “vasocentric” disease compared to classical ARDS (although the pulmonary microcirculation is clearly affected in classical ARDS as well). Computational models of deranged pulmonary microcirculatory function have been able to reproduce the depth of hypoxemia observed in COVID-19 ARDS in the absence of significant pure shunt [6].

Nevertheless, before generalizing the results of Chiumello et al. it's important to note that the sample size studied was very small ($n=32$). Crucially, it seems doubtful that the patients enrolled in the study by Chiumello et al. are typical of COVID-19 ARDS patients more generally. In their cohort, the median compliance was 50 mL/cmH₂O, a value substantially higher than generally observed in recent studies of COVID-19 ARDS which have reported median values for static compliance that are considerably lower: 27 mL/cmH₂O ($n=257$) [7], 28 mL/cmH₂O ($n=267$) [8], 35 mL/cmH₂O ($n=296$) [9], 41 mL/cmH₂O ($n=301$) [10], and 32 mL/cmH₂O ($n=533$) [11], similar to values in patients with classical ARDS [12] (Fig. 1). The differences between the 32 patients and these results (total $n=1654$) cannot be explained by the timing of the Crs measurements since these values were also obtained at baseline. These differences also cannot be explained by differences in the level of positive end-expiratory pressure (PEEP) at which compliance was measured (5 cmH₂O, in Chiumello's study;

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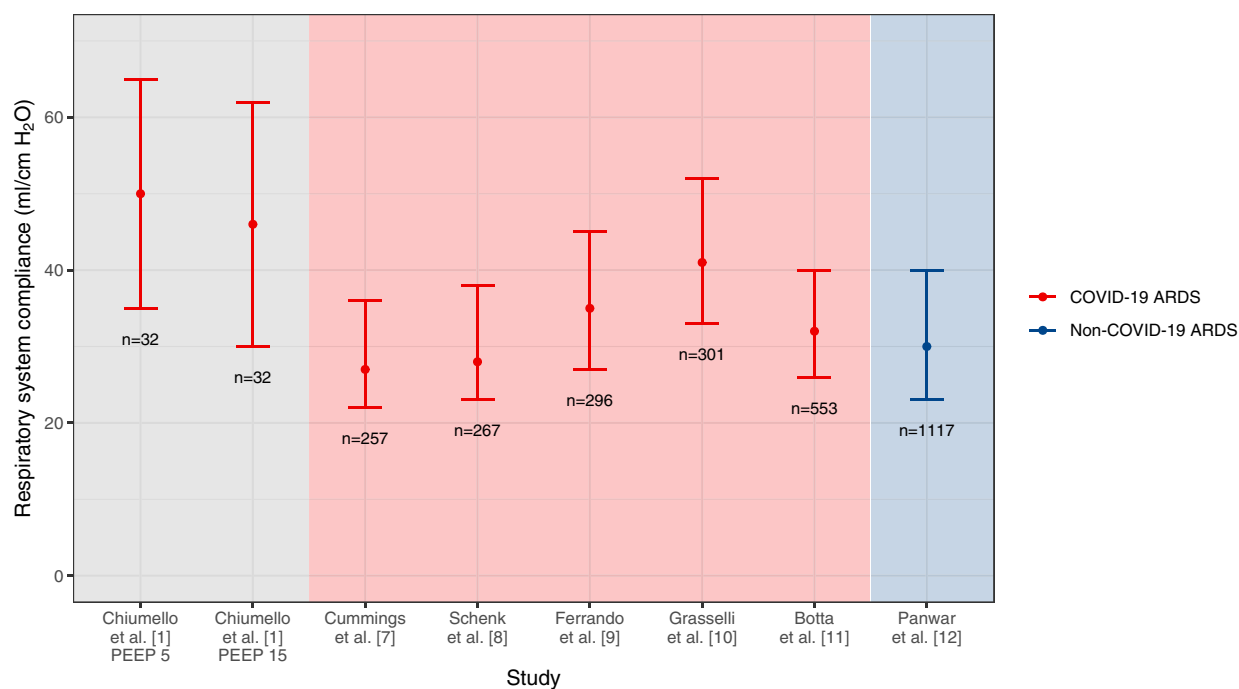


Fig. 1 Distribution of respiratory system compliance in the study of COVID-19 ARDS reported by Chiumello et al. in other studies of COVID-19 ARDS, and in non-COVID-19 ARDS. Error bars represent standard deviations (for Chiumello et al.) or interquartile ranges (for all other studies)

“clinical values of PEEP” in the other studies) since when Chiumello increased PEEP to 15 cmH₂O, the median Crs was approximately 46 ml/cmH₂O, still substantially higher than the >1600 COVID-19 patients from the other studies. We might therefore regard the patients in the study by Chiumello et al. as an “atypical subset of COVID-19 ARDS.”

In any case, we may ask, “So what?” even if COVID-19 ARDS were an atypical subset of ARDS (and it’s not clear that this is indeed the case), should this prompt any changes to management? The “vasocentric” pathophysiology demonstrated in this and many other studies suggests a potential role for vascular interventions such as therapeutic anticoagulation [13]; relevant clinical trials are ongoing. An important question is whether the findings of this study suggest any changes in ventilatory management. Chiumello et al. contend that their findings argue against the use of a “higher” PEEP ventilation strategy in the early phase of COVID-19 ARDS. In their study, hypoxemia was not primarily the consequence of atelectasis and increases in PEEP were associated with signs of overdistention (reduced compliance, unchanged/worsened dead space) despite a substantial improvement in oxygenation. Unfortunately, they did not directly quantify the degree of lung recruitment by CT scan. Other studies in COVID-19

ARDS have reported varying degrees of lung recruitability [14, 15]. The lower compliance observed in the patients from the other studies suggests (Fig. 1) that many patients with COVID-19 ARDS may have substantial potential for lung recruitment.

It is widely appreciated that ARDS is a heterogeneous disorder and that many patients with ARDS may have little or no potential for lung recruitment [16–18]. Higher PEEP may well be harmful in such patients whether or not they have COVID-19 [19]. The findings of Chiumello et al. should alert clinicians to the fact that, given the pulmonary vascular dysfunction associated with COVID-19 ARDS, a positive oxygenation response to an increase in PEEP does not necessarily indicate recruitment of atelectatic lung in these patients; other techniques for assessing lung recruitment should be considered [20]. Nevertheless, none of the findings of this study provide any reason to believe that the standard approach to the management of ARDS should be modified for severe COVID-19. Rather, clinicians should continue to follow the accepted evidence-based framework for managing ARDS including COVID-19 ARDS. Unsafe lung stress and strain should be avoided by maintaining lower tidal volumes and driving pressures. Patients with more severe hypoxemia should be ventilated in the prone position, and PEEP should be carefully selected to maintain acceptable

oxygenation while minimizing overdistention of the baby lung.

In conclusion, until we have evidence to the contrary, we believe that ARDS patients with the same mechanical and clinical characteristics should be ventilated in the same way, without regard to whether they have COVID-19 ARDS or classical ARDS.

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Compliance with ethical standards

Conflicts of interest

ECG reports receiving personal fees and research support in the form of equipment from Getinge and research support in the form of equipment from Timpel. ASS reports receiving personal fees from Baxter and Novalung/Xenios.

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