

Pathophysiology of COVID-19-associated acute respiratory distress syndrome

Authors' reply

Luigi Camporota and colleagues and Vasiliki Tsolaki and colleagues challenge our finding that suggests that patients with COVID-19 have a form of injury that is encompassed by the conceptual model of acute respiratory distress syndrome (ARDS). The argument used by Camporota and colleagues and Tsolaki and colleagues is that the median static compliance we observed in patients with COVID-19-associated ARDS (41 mL/cm H₂O) was significantly higher compared with patients with classical ARDS. However, they miss the point that the distribution of compliance in patients with COVID-19 ARDS was wide and only 17 (6%) of 297 patients had compliance greater than the 95th percentile of the classical ARDS cohort. Thus, one cannot discriminate COVID-19 ARDS from classical ARDS on the basis of values of compliance. Moreover, studies now totalling well over 1000 patients with COVID-19 ARDS report values of compliance (27 mL/cm H₂O,¹ 35 mL/cm H₂O,² 28 mL/cm H₂O,³ and 32 mL/cm H₂O⁴) that are consistent or even lower than the values observed by Chiumello and colleagues (48 mL/cm H₂O [SD 16] and 42 mL/cm H₂O [14])^{5,6} and Gattinoni and colleagues (44 mL/cm H₂O [17])⁷ in classical ARDS. In addition, Panwar and colleagues recently showed that patients with classical ARDS had a wide range of compliance, with about one in eight patients (136 [12.2%] of 1117 patients) having compliance of at least 50 mL/cm H₂O, and that the ratio of partial pressure of arterial oxygen to fractional concentration of oxygen in inspired air (PaO₂/FiO₂) and static compliance were almost completely dissociated.⁸ We used a linear regression model

to analyse the relationship between static compliance and PaO₂/FiO₂ in COVID-19 ARDS⁹ and in classical ARD.¹⁰ This analysis can be quantified in terms of R² (ie, the percentage of the PaO₂/FiO₂ variation that is explained by changes in compliance) and p values (to test the null hypothesis—ie, that the equation coefficient is equal to zero and that changes on PaO₂/FiO₂ have no effect on changes in compliance). In COVID-19 ARDS, the relationship was not significant (p=0.160) and R² was 0.007 (appendix). In classical and pneumonia ARDS, results were statistically significant (p<0.0001) but values of R² were low (0.059 and 0.040, respectively; appendix). Thus, only 6% of the variability of PaO₂/FiO₂ is explained by the variability of compliance (p<0.0001), meaning the remaining 94% of the variability of PaO₂/FiO₂ depends on something else.

We agree with Camporota and colleagues and Tsolaki and colleagues that positive end-expiratory pressure (PEEP) should be individualised to the specific patient in COVID-19 ARDS, as in all other patients with ARDS. We believe the current methods, such as the lower PEEP–high FiO₂ table, should be used until evidence of improved outcomes with other explicit strategies becomes available.

Although from the perspective of clinical utility, it is easier to use a dichotomised variable, we agree with Ananthu Narayan and colleagues that grouping a patient population according to dichotomisation of continuous variables can lead to loss of information. We retrospectively analysed our data and found that values identified by the receiver operating characteristics curve methods were similar to the median values of compliance and D-dimers used in our study (data not shown). However, the retrospective nature of this analysis limits its validity and suggest that prospective studies are required to validate this approach. Moreover, the influence of D-dimer and static compliance on survival was

assessed using a Cox proportional hazard model using sequential organ failure assessment (SOFA) score, sex, age, and PaO₂/FiO₂ as variables.⁹ Regarding the potential imbalance in the distribution of potential confounders, values of SOFA score at baseline and use of steroids and anticoagulation did not vary among our four patient groups.⁹ We also acknowledge that ventilatory ratio is only a proxy of dead space fraction and that other methods are available to measure specifically this relevant parameter, and that chest CT scans were obtained only in a small number of patients based on compelling clinical indications.

Finally, we agree with Michael Dandel that, given the relevant role of filling defects or occlusions of the pulmonary vasculature, particular attention should be paid to right ventricular dysfunction in patients with COVID-19 ARDS.

GG reports personal fees and non-financial support from Getinge and Biotest; personal fees from Thermofisher and Draeger Medical, and grants and personal fees from Fisher&Paykel, outside of the submitted work. AP reports personal fees from Maquet, Novalung/Xenios, Baxter, and Boehringer Ingelheim, outside of the submitted work. All other authors declare no competing interests.

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Lancet Respir Med 2020
Published Online
November 13, 2020
[https://doi.org/10.1016/S2213-2600\(20\)30525-7](https://doi.org/10.1016/S2213-2600(20)30525-7)
See Online for appendix

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