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Authors response: “Clinical characteristics, physiological features, and outcomes associated with hypercapnia in patients with acute hypoxemic respiratory failure due to COVID-19—Insights from the PRoVENT-COVID study”

In one of the analyses of our observational study named ‘Practice of VENTilation in COVID-19 patients’ (PRoVENT-COVID), we showed that hypercapnia has associations with development of acute respiratory distress syndrome (ARDS) and the occurrence of venous thromboembolic events. The analysis also indicated that hypercapnia has associations with the ventilatory ratio and length of hospital stay.

Bhattacharya and colleagues correctly state that ‘lung-protective ventilation’ is the cornerstone of management of patients with ARDS. We would like to stress, however, that this strategy does involve the use of a lower tidal volume and airway pressure, and not the use of a higher respiratory rate [1]. While we agree that use of lower tidal volume could result in the need for using a higher respiratory rate, an increase in rate can be prevented by applying another important lung-protective strategy named ‘permissive hypercapnia’, an often-forgotten part of the tested intervention in the seminal ARMA trial [2]. We should also note that use of a higher respiratory rate has been shown to have associations with worse outcomes [3].

With regard to the notion that hypercapnia occurred more often in obese patients, and the suggestion of the ‘obesity paradox’ we would like to refer to another analysis of PRoVENT-COVID, wherein we showed that mortality was not higher and lung-protective ventilation was applied similarly in overweight and obese patients compared to normal-weight patients [4]. We appreciate Bhattacharya and colleagues’ suggestion to explore the association of the ventilatory ratio with outcomes, and refer to yet another analysis of the database, wherein we showed that multiple dead space estimates, including ventilatory ratio, were not independently associated with mortality at day 28 [5].

Lastly, we agree that it could be helpful to dive deeper into the association of oxygenation with outcomes in patients with ARDS in general, and in patients with COVID-19 ARDS in particular. This analysis is complex, and is also affected by effects of the applied positive end-expiratory pressure (PEEP). Indeed, higher PEEP increases the amount of aerated lung, and with that leads to an increase in alveolar ventilation. We recently showed this to be true also in patients with COVID-19 ARDS, but also showed that this approach has an association with worse outcomes, possibly related to hemodynamic side-effects of higher PEEP [6].

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Declaration of Competing Interest

The authors have no conflicts of interest to report.

References

- [1] Rhodes A, et al. Surviving Sepsis campaign: international guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med.* 2017;43(3):304–77.
- [2] Acute Respiratory Distress Syndrome, N, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med.* 2000;342(18):1301–8.
- [3] Costa ELV, et al. Ventilatory variables and mechanical power in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2021;204(3):303–11.
- [4] Schavemaker R, et al. Associations of body mass index with ventilation management and clinical outcomes in invasively ventilated patients with ARDS related to COVID-19-insights from the PRoVENT-COVID study. *J Clin Med.* 2021;10(6).
- [5] Morales-Quinteros L, et al. Dead space estimates may not be independently associated with 28-day mortality in COVID-19 ARDS. *Crit Care.* 2021;25(1):171.
- [6] Valk CMA, et al. Association of early positive end-expiratory pressure settings with ventilator-free days in patients with coronavirus disease 2019 acute respiratory distress syndrome: a secondary analysis of the practice of VENTilation in COVID-19 study. *Eur J Anaesthesiol.* 2021;38(12):1274–83.

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