Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

14. Gordon DE, Jang GM, Bouhaddou M, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature* 2020; **583**: 459–68
15. Lucchetta V, Bonvicini D, Ballin A, Tiberio I. Propofol infusion syndrome in severe COVID-19. *Br J Anaesth* 2020; **125**: e441–2
16. Soh M, Hifumi T, Isokawa S, Shimizu M, Otani N, Ishimatsu S. Neuroleptic malignant syndrome in patients with COVID-19. *Am J Emerg Med* 2020; **38**: 2243. e1–3

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Characterising the pulmonary response to prone positioning. Comment on *Br J Anaesth* 2021; 126: 48-55

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Editor—Weiss and colleagues[1] recently published a detailed report on prone positioning during the coronavirus disease 2019 (COVID-19) pandemic. Prone positioning has been widely adopted both in intubated and non-intubated patients with respiratory failure. The response falls into four broad categories of *P/F* ratio change: no (or worse) change, improvement that is sustained on returning supine, improvement that is slightly diminished on return to supine, or improvement that is greatly diminished on return to supine.[2]

The main outcome reported was that prone positioning improved *P/F* ratio from 17.9 to 28.2 kPa after 81 (range: 61–119) min (immediate) across 36 subjects, of which 26 had a response of ≥20%. Results from 32 subjects indicate that the response persisted on return to supine (sustained). The immediate response to this first manoeuvre did not predict those who would survive. As the authors mentioned, van Meenen and colleagues[3] also reported lack of prognostic capacity of changes in *P/F* ratio to prone positioning in acute respiratory distress syndrome (ARDS) not attributable to COVID-19. However, this group compared *P/F* ratio values before prone positioning to those on return to supine (sustained), whereas Weiss and colleagues compared P/F ratio values before prone positioning to values whilst prone (immediate). It would be interesting to report if a sustained response was related to favourable outcome in the Weiss and colleagues COVID-19 cohort.

Measurement of immediate response to prone positioning is common in the published literature, with response usually defined as an increase in P/F ratio of ≥20% or by 20 mm Hg (2.7 kPa).[2] These are arbitrary criteria and cannot be utilised at the bedside. Although relatively easy to calculate, the *P/F* ratio encompasses a complex interaction between haemoglobin concentration, oxygen extraction, and pulmonary shunt fraction, making it sensitive to relatively small changes in FiO_2 whilst not accounting for PEEP or mean airway pressures.

The lack of association between immediate response to prone positioning and favourable outcome reported by Weiss and colleagues[1] is consistent with some pre-COVID-19 data. For example, in a reanalysis of the landmark Proning Severe ARDS Patients study,[4] no markers of gas exchange predicted those who would survive or not after initial prone positioning.[5] Here, 91% of subjects who were in the worst quintile for initial *P/F* ratio change (which ranged from −81 to −1 mm Hg or 10.8 to −0.1 kPa) survived. Other data illustrated no difference in *P/F* ratio between survivors and non-survivors after the first prone manoeuvre in 225 patients.[6] This presents a challenge to those caring for patients with COVID-19, as promising initial improvements in gas exchange might not translate into favourable clinical outcomes.

In the current report, death or progression to extracorporeal membrane oxygenation was more frequent in those displaying a diminished response to further prone manoeuvres. There are limited data on other factors that might have prognostic value based on response to prone positioning. Reduction in $Paco_2$ after a single episode of prone positioning was associated with improved 28-day survival (relative risk: 1.48; 95% confidence interval: 1.07–2.05; P=0.02), despite a trend for increasing $Paco_2$ in all patients over subsequent prone manoeuvres.[6] Decreases in $Paco_2$ of ≥1 mm Hg have previously been used to describe responders.[2] The ventilatory ratio can approximate dead-space ventilation and has shown predictive utility in ARDS patients, where initial measurement was higher in non-survivors than survivors (2.02 [0.8] *vs* 1.75 [0.5]; P<0.001).[7] Ventilatory ratio might be physiologically relevant

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in patients with COVID-19 pneumonitis, as increased dead-space ventilation might be predicted if micro- and macro-thrombus burden is high. This was observed in the present report and by others who compared COVID-19 and non-COVID-19 cohorts.[8] However, this is not a consistent finding,[9] and ventilatory ratio response to prone positioning showed little predictive utility in the present study or in other data.[10]

Taken together, this important study showed that using the immediate response in *P*/*F* ratio upon prone positioning may be of limited utility in predicting outcome. However, the report provides evidence that diminishing response might be an important pattern to realise at the bedside for COVID-19. Evidence to support the optimal proning strategy, particularly in the context of COVID-19, is important. Further work could focus on trying to establish other characteristics or patterns that predict not only the likelihood of ongoing response to prone positioning, but also the likelihood of favourable outcome to help guide resource/personnel allocation and decision-making at the bedside.

Declarations of interest

The author declares that they have no conflicts of interest.

References

1. Weiss T, Cerda F, Scott B, et al. Prone positioning for patients intubated for severe acute respiratory distress syndrome (ARDS) secondary to COVID-19: a retrospective observational cohort study. *Br J Anaesth* 2021; **126**: 48–55
2. Koulouras V, Papathanakos G, Papathanasiou A, Nakos G. Efficacy of prone position in acute respiratory distress syndrome patients: a pathophysiology-based review. *World J Crit Care Med* 2016; **5**: 121–36
3. van Meenen DM, Roozeman JP, Serpa Neto A, et al. Associations between changes in oxygenation, dead space and driving pressure induced by the first prone position session and mortality in subjects with acute respiratory distress syndrome. *J Thorac Dis* 2019; **11**: 5004–13
4. Guérin C, Reignier J, Richard J, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013; **368**: 2159–68
5. Albert R, Keniston A, Baboi L, Ayzac L, Guérin C. Prone position-induced improvement in gas exchange does not predict improved survival in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2014; **189**: 494–6
6. Gattinoni L, Vagginelli F, Carlesso E, et al. Decrease in $PaCO_2$ with prone position is predictive of improved outcome in acute respiratory distress syndrome. *Crit Care Med* 2003; **31**: 2727–33
7. Sinha P, Calfee C, Beitler J, et al. Physiologic analysis and clinical performance of the ventilatory ratio in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2018; **199**: 333–41
8. Chiumello D, Busana M, Coppola S, et al. Physiological and quantitative CT-scan characterization of COVID-19 and typical ARDS: a matched cohort study. *Intensive Care Med* 2020; **46**: 2187–96
9. Grieco D, Bongiovanni F, Chen L, et al. Respiratory physiology of COVID-19-induced respiratory failure compared to ARDS of other etiologies. *Crit Care* 2020; **24**: 529
10. Sidhu G, Deutsch E, Bogdan N, et al. Ventilatory ratio with proning in COVID-19 ARDS patients: a new tool for an old strategy. *Crit Care Med* 2020; **49**: 133

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