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*Letter to the Editor*

**Reply to: Awake prone positioning in non-intubated patients with acute hypoxemic respiratory failure due to COVID-19: A systematic review of proportional outcomes comparing observational studies with and without awake prone positioning in the setting of COVID-19.**

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### Correspondence

**Reply to: Awake prone positioning in non-intubated patients with acute hypoxemic respiratory failure due to COVID-19: A systematic review of proportional outcomes comparing observational studies with and without awake prone positioning in the setting of COVID-19.**

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We have read with great interest the study by Pavlov, et al (1) where the authors conducted a systematic review (SR) of observational studies evaluating awake prone positioning (AP) for patients with COVID-19 and hypoxemic respiratory failure (HRF). The results of this SR do not support a reduction in intubation rate associated with AP despite improved oxygenation. We applaud the authors' efforts in conducting this study, although we would like to point out a few considerations.

The prone position has been shown to improve oxygenation in patients under mechanical ventilation with acute respiratory distress syndrome (ARDS) (2). The interest on AP grew rapidly with the COVID-19 pandemic since this is a low-cost intervention that can improve oxygenation through diverse physiological mechanisms in conscious COVID-19 patients receiving oxygen therapy (3). However, its precise usefulness remains to be elucidated in well-designed randomized controlled trials (RCT) and most evidence to date can only be drawn from observational studies.

We worry that the SR by Pavlov, et al. could have been left outdated at the moment of its publication since the authors included studies available up to August 15, 2020. In the recently published observational APRONOX study of AP, a complimentary systematic search of the literature (published and pre-prints) was conducted up to June 8, 2021 with a meta-analysis (MA); observational studies of AP were found to support a decreased intubation rate and mortality in patients with COVID-19 (4). Even when these results were not arrived at through a formal SR like the one by Pavlov and cols., most of the studies meeting inclusion criteria (observational studies of AP with a comparison group with enough data available to calculate intubation rates) were made available from late 2020 to 2021, reflecting that an important

number of observational studies of AP have been published after August 2020. In a different SR with MA, Chu, et al. found a lower mortality rate for patients under AP despite no apparent reduction in intubation rate in a similar study period (5). Even when the potential shortcoming of the time period in the study by Pavlov, et al. could be addressed by future SR or by reviewing multiple SR in an umbrella review, this should highlight the importance of conducting and publishing evermore “rapid living systematic reviews” (6), especially for rapidly changing areas of research like COVID-19.

Pavlov and cols. must be recognized for reviewing abstracts in both English and Chinese. However, we noted that some of the authors are based at institutions in France, Canada, Mexico, and Spain. We wonder if the authors could have done an extra effort to review also abstracts in French and Spanish, thereby taking advantage of their multinational group of authors to reach a more compelling and comprehensive study. By doing this, the authors would have tackled better one of the main barriers of science: the language barrier (7).

Evidence from RCT evaluating AP is urgently needed. However, researchers intending to investigate AP should be warned that evaluating this intervention could be more complex than it seems. The recently published PROFLO trial (8) is a good example since patients in both the intervention and control group ultimately had at least some amount of exposition to AP (median 9.0 and 3.4 hours/day, respectively) with few patients in the intervention group reaching the goal of  $\geq 16$  hours/day in AP (6%), which alongside the small sample size could explain why no differences in intubation rates were observed in this trial.

When enough evidence from RCT assessing AP is available, SR and MA will be helpful to picture the usefulness of AP for patients with HRF and COVID-19. It will be important to contrast the results of SR and MA of observational studies like the one performed by Pavlov, et al. (no difference in intubation rate), Chua, et al. (no difference in intubation rate, but lower mortality rate) or the APRONOX group (decreased intubation rate) since associations from MA of observational studies and RCT have been found to be opposite in direction in 37.1% of cases (9).

Showing that prone positioning was useful for specific patients with ARDS on mechanical ventilation took several years and RCT. We now know that prone positioning is useful when started early, for patients with moderate-to-severe ARDS, under protective-ventilation strategies (10). Therefore, it could be too early to elaborate conclusions on AP since there is still a long road ahead to identify patients and circumstances in whom AP could be an effective intervention for HRF.

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