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EDITORIAL

Prone positioning during extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. Pro

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Building solid evidence in intensive care medicine is challenging, mostly due to patient heterogeneity and concomitant treatment interactions. In the context of acute respiratory distress syndrome (ARDS), only two interventions have demonstrated a positive impact on patient survival with high quality of evidence. The first is a low-tidal volume, low-plateau pressure ventilation [1], and the second is prone positioning (PP) of patients with moderate-to-severe hypoxemia [2]. The latter recommendation was achieved after a long journey marked by trials that failed for various reasons, including insufficient sample size, [3] relatively short duration of the PP cycles, [4, 5] patient selection criteria [4–6], and inadequate ventilation strategy. Guerin et al. [2] discovered the "optimal formula" for PP, emphasizing its early application combined with low-tidal volume ventilation, muscle relaxants, and prolonged sessions lasting at least 16 h. Most importantly, they implemented PP only in patients with more severe hypoxemia, defined as PaO_2 to FiO_2 ratio below 150 mmHg after a stabilization period with standardized ventilation settings. The most hypoxemic patients usually present a smaller end-expiratory lung volume ("baby lung") due to a higher amount of collapse in the dependent lung regions [7]. Prone positioning is associated with a redistribution and homogenization of ventilation from ventral to dorsal lung regions, thus mitigating the risk of overdistension of nondependent zones and facilitating the reopening of poorly aerated or collapsed dependent regions. These changes result in a reduction of intrapulmonary shunt fraction and in a better matching of ventilation and perfusion, which in turn translates into an improvement of oxygenation.

The most severe ARDS patients may present a refractory impairment of gas exchange and/or lung mechanics, so that the use of extracorporeal respiratory support (extracorporeal membrane oxygenation, ECMO) is proposed to maintain viable blood oxygenation and to facilitate the application of protective ventilation settings. After ECMO start, an "ultraprotective" ventilation strategy is commonly adopted, to allow lung rest and reduce the risk of ventilation-induced lung injury. However, ultraprotective ventilation strategies might increase the risk of collapse in dependent lung regions. In addition, prolonged use of neuromuscular blockers and positive fluid balance could further contribute to a loss of aeration in dorsal regions. In this context, PP during ECMO might contribute to reopen collapsed dorsal regions and to mitigate the risk of ventilator-induced lung injury. Consequently, it is plausible that PP may be beneficial even after the initiation of ECMO support (see Fig. 1).

Historically, PP has been employed sporadically during ECMO, due to concerns about potential complications, particularly the dislodgement of ECMO cannulae and bleeding. In the last decade, PP has been succesfully implemented and increasingly used in many ECMO centers worldwide. The combination of ECMO and PP is justified by the abovementioned physiological rationale and supported by the findings of several observational studies, that showed improvements in oxygenation and respiratory mechanics [8, 9], with a very low incidence of adverse events attributable to PP[10]. In 2022, a comprehensive systematic review and meta-analysis [11] of observational data from 1836 patients showed an association between the use of PP during ECMO and reduced mortality. In the same year, an individual patient meta-analysis [10] on 889 patients reported a non-significant

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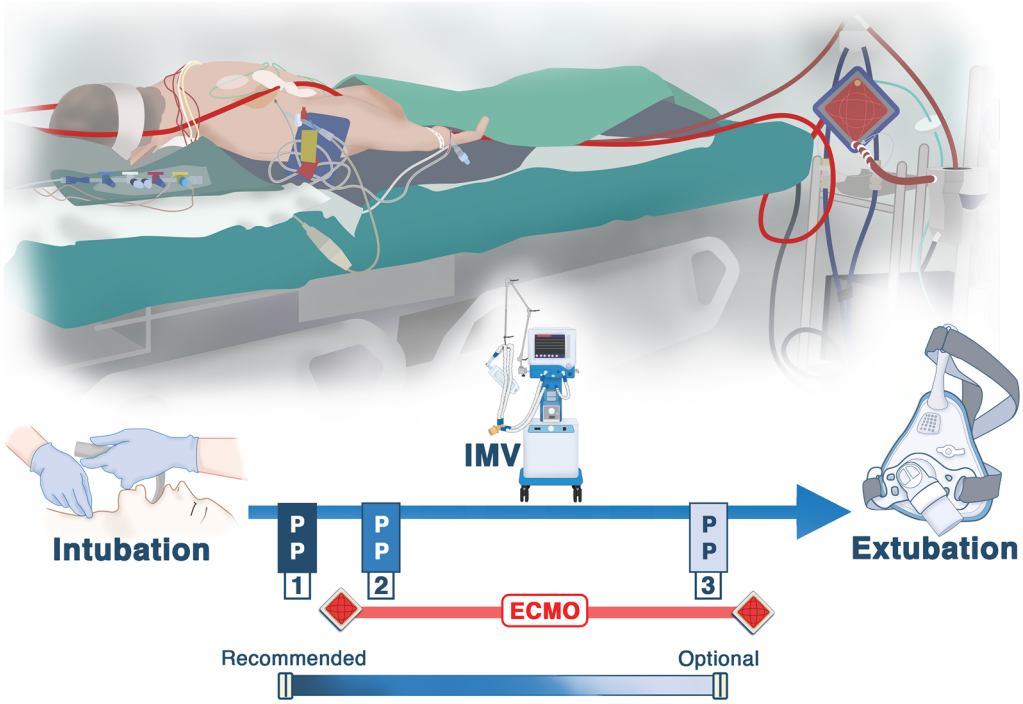

Fig. 1 Prone position in mechanically ventilated patients with severe ARDS with ECMO support. *PP* prone position; *IMV* invasive mechanical ventilation; *ECMO* extracorporeal membrane oxygenation. Timepoints of PP in severe ARDS patients: (1) before ECMO; (2) early PP during ECMO; (3) late PP during ECMO

association between PP during ECMO and ICU mortality (adjusted hazard ratio 0.67, 95% confidence interval: 0.42–1.06). However, after propensity score matching, the survival analysis showed a lower 60-day mortality in the prone group ($p=0.002$). More recently, a secondary analysis of the EuroPronECMO study[12] has shown that the timing of prone positioning (PP) during ECMO may also have an impact. Patients receiving PP in the early phase of ECMO support were more likely to be discharged alive from the intensive care unit compared to those in whom PP was implemented later.

In December 2023, Schmidt et al. published the results of the first randomized controlled study (PRONECMO trial) assessing the impact of PP during ECMO on patient outcome [13]. Among 170 patients with severe ARDS on venovenous ECMO, PP, when compared with supine positioning, did not result in a significant reduction in the time to successful weaning from ECMO—the primary outcome of the study. Moreover, no differences were observed within 90 days in ECMO duration, intensive care unit (ICU) length of stay, or mortality. This negative results may be attributed to several factors. Firstly, nearly all patients had ARDS due to coronavirus disease 2019 (COVID-19), a disease which might exhibit peculiar pathophysiological alterations [14]. Moreover, respiratory system compliance recorded after the return to supine position after PP was not increased compared to that measured before the PP cycle, which is in contrast with previous reports of early application of PP during ECMO in non-COVID-19 ARDS[12]. Consequently, these findings might not be readily generalizable to ARDS from other etiologies, such as bacterial pneumonia. Secondly, as per the study design, PP was uniformly administered to all patients in the prone group, regardless of their clinical characteristics post-ECMO cannulation. To date, it remains unknown whether specific clinical characteristics, such as potential for lung recruitment or risk of overdistention, could identify subgroups of patients that would benefit more from PP during ECMO. This may at least in part explain the different results of previous observational studies, wherein PP was employed only when deemed clinically indicated by the attending physicians.

In January 2024, Tong et al. published the results of a randomized trial [15] exploring whether PP implemented within 24 h of ECMO improves survival in ARDS patients. The study included 97 patients, half with COVID-19. The authors reported that PP resulted in improved oxygenation and respiratory mechanics, and

was associated with significantly higher 30-day and hospital survival rates. However, concerning inconsistencies were found between the text and the reported survival analysis. Moreover, the trial was not prospectively registered on an international clinical trial registry platform. For these reasons, the latter study findings must be interpreted with caution.

In conclusion, literature data are conflicting and current evidence is not sufficient to support the routine application of PP during ECMO, despite the sound pathophysiological rationale. However, available evidence consistently indicates that the procedure, when performed in experienced and highly specialized ECMO centers, is feasible and, more importantly, safe, without signal of harm associated with the intervention. While waiting for more conclusive data from ongoing studies, we believe that PP, when performed in experienced centers, remains a promising treatment option for ARDS patients on venovenous extracorporeal support.

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