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EDITORIAL

Prone positioning during VV ECMO: stay on the back or not?

Asger Granfeldt[1,2*] and Ghislaine Douflé[3,4]

Following decades of research and several clinical trials, the PROSEVA trial provided evidence of the beneficial effect of prone position, which is now considered standard of care for patients with moderate-to-severe Acute Respiratory Distress Syndrome (ARDS) [1, 2]. Prone positioning was initially considered a complex clinical procedure associated with potential life-threatening complications [3]. However, with time and with the resource limitations imposed by the COVID-19 pandemic, the uptake of prone positioning has significantly increased over the years. In patients with severe and refractory ARDS not responding to conventional therapies and prone positioning, venovenous extracorporeal membrane oxygenation (VV ECMO) is strongly recommended [1]. It is generally accepted that evidence-based interventions for the management of ARDS such as lung protective ventilation should be continued during VV ECMO, yet this is sparsely studied [4]. Patients on VV ECMO differ from those with moderate-to-severe ARDS in several ways, including lack of response to proning prior to ECMO initiation, a potential higher risk of adverse effects, and the application of ultra-protective ventilation, which makes it unclear whether the protective benefits of prone positioning persists on VV ECMO (Fig. 1).

Pettenuzzo and colleagues conducted a systematic review, and meta-analysis on prone positioning during VV ECMO summarizing the evidence on the topic [5]. The review was thoroughly conducted according to guidelines for systematic reviews ensuring rigorous methodology. The review identified 22 studies divided into 20 observational studies and 2 randomized-controlled trials. In the meta-analysis of the primary outcome (28-day mortality), prone positioning was associated with a lower mortality (OR 0.64, 95% CI 0.42–0.98). However, this analysis was based solely on observational studies. The first randomized trial by Tong et al. included 97 patients and showed improved survival with prone positioning at 30 days, although this effect disappeared over time with no apparent effect at 50 days. [6] In the largest and most rigorous randomized trial to date including 170 patients, prone positioning demonstrated no protective effects on neither primary nor secondary outcomes [7]. This discrepancy illustrates two essential points, the importance of outcome selection and differences between observational and randomized-controlled trials. In both randomized-controlled trials, survival curves illustrated a change in survival around 30 days, with no difference with prolonged follow-up. Hence, selecting an early outcome in patients on VV ECMO who have prolonged ICU and hospital stay and where the most common cause of death is discontinuation of life-sustaining therapy may not be optimal [8]. This is also illustrated by the systematic review by Pettenuzzo [5] where a significant difference was found in hospital mortality and 28-day mortality but not in 60-day, 90-day, or 6-month mortality.

Second, the review is an illustrative example of difficulties in interpreting findings when observational studies contradict randomized trials pertaining to the same topic. Observational studies are inherently prone to bias and unmeasured confounding and studies on the topic have demonstrated that observational studies systematically and substantially overestimate mortality benefits when compared to randomized trials investigating the same question [9, 10].

*Correspondence: granfeldt@clin.au.dk
[1] Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
Full author information is available at the end of the article

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Fig. 1 Prone positioning during VV ECMO: stay on the back or not?

Additionally, change in clinical practice over time, in this case higher rate of prone positioning before ECMO, may have confounded the findings by Pettenuzzo et al. Indeed, in the EOLIA trial, prone positioning was performed in approximately 60% of patients prior to VV ECMO. Similarly, in their systematic review, Pettenuzzo et al. reported a proning rate of 51% prior to ECMO initiation, while 98.8% of the patients were proned before ECMO in the prone positioning group of the PRONECMO trial [7]. This illustrates that prone positioning has become standard therapy prior to VV ECMO and can explain the contrasting findings between observational and randomized-controlled trials. Indeed, in the current review, prone positioning on ECMO was linked to better short-term survival in patients that had not been proned prior to VV ECMO and in older studies, which would be expected, as patients who did not respond to proning and eventually required ECMO were also less likely to respond to proning once on ECMO. One may even speculate that patients not proned before ECMO might not have required VV ECMO had they been proned in the first place. However, the current evidence does not address this question.

An important aspect of prone positioning is safety. Although some adverse events (such as bleeding of cannula site, circuit change, and thromboembolism events) were more frequent with prone positioning, these events were only reported by a very limited number of studies and there was no difference in the overall incidence of bleeding events. The low number of studies reporting adverse events illustrates a general concern with regards to rigorous reporting of adverse events [11].

Since the COVID-19 pandemic, clinical trials, observational studies, and systematic reviews have included patients with and without COVID-19. The question remains whether COVID-19 represents a specific phenotype that responds differently to interventions otherwise proven effective. In a recent randomized-controlled trial investigating the effect of inhaled sedation in patients with ARDS, the treatment response differed between non-COVID-19 and COVID-19 patients [12]. In the randomized-controlled trial on prone positioning on ECMO trial by Schmidt et al., 94% of the patients had ARDS related to COVID-19 which may explain the lack of effect. [7] This is also supported by a subgroup analysis in the randomized-controlled trial by Tong et al. demonstrating no effect in the subgroup of patients with COVID-19, albeit with a low number of patients [6]. Data from observational studies identified in the current review also found that non-COVID-19 was associated with a greater benefit from prone positioning.

For the clinician, the question remains whether to prone patients on VV ECMO or not. Based on the current review, there is insufficient evidence to recommend prone positioning as standard practice. The protective effect shown in the current review is based on observational studies prone to bias and confounding, the use of short-term outcomes, and inclusion

of older studies with lower use of prone positioning prior to ECMO. Nevertheless, prone positioning is an intervention without significant costs and with limited adverse events (including in ECMO patients) that could easily be applied to selected patients in specialized centers.

Author details
[1] Department of Clinical Medicine, Aarhus University, Aarhus, Denmark. [2] Department of Anesthesiology and Intensive Care, Aarhus University Hospital, Aarhus, Denmark. [3] Interdepartmental Division of Critical Care Medicine of the University of Toronto, Toronto, Canada. [4] Department of Anesthesia and Pain Management, Toronto General Hospital, Toronto, Canada.

Declarations

Conflicts of interest
None.

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