Prone Positioning of Patients during Venovenous Extracorporeal Membrane Oxygenation

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The EOLIA (ECMO to Rescue Lung Injury in Severe ARDS) trial (1), together with subsequent secondary analyses of trial data (2, 3), demonstrated a survival benefit with the use of venovenous extracorporeal membrane oxygenation (ECMO) in patients with severe acute respiratory distress syndrome (ARDS) who fail conventional ventilation management, including prone positioning (PP). However, mortality with ECMO for ARDS remains high, and substantial gains in patient outcomes may yet be realized through further refinements in the clinical application of venovenous ECMO.

Prolonged PP for patients with ARDS and a ratio of arterial oxygen partial pressure to fractional inspired oxygen less than 150 has been shown to improve mortality (4, 5). Although improvement in oxygenation as a result of an improved matching of ventilation and perfusion matching is common with PP, reduction of ventilator-induced lung injury via reduction of the stress and strain across the lungs appears to be the primary mechanism of benefit (6) and independent of improvements seen in gas exchange (7).

The ability of venovenous ECMO to facilitate an advanced degree of lung protection not achievable by conventional means appears to underlie its potential benefit. Lung protection above and beyond what was achieved in the ECMO arm of EOLIA may help further improve the 35% 60-day mortality reported in the trial. Near-apneic and apneic ventilation strategies that substantially reduce driving pressure and mechanical power represent one approach that has been tested in pilot mechanistic studies (8–10). Similarly, it is possible that PP of patients while they are receiving venovenous ECMO may have a synergistic effect with ultraprotective lung ventilation to improve patient outcomes, as it does with lung-protective ventilation in patients not receiving ECMO.

In this issue of AnnalsATS, Giani and colleagues (pp. 495–501) report results of their multicenter, retrospective cohort study assessing the physiologic effects of PP during venovenous ECMO as well as hospital mortality in a propensity score–matched analysis (11). The prone group (n = 107) consisted of patients from four centers where PP during venovenous ECMO support was routine. Patients from two centers managing patients supine during ECMO served as control subjects (n = 133). The time from ECMO initiation to the first PP session was 4 days (range, 2–7 d). Overall, a total of 326 PP maneuvers were examined, and the mean duration of PP was 15 hours (range, 12–18 h). There were no major complications recorded. Significant improvement in intrapulmonary shunt fraction, ratio of arterial oxygen partial pressure to fractional inspired oxygen, and static compliance were seen during PP, and the improvement was maintained after turning them supine. In a propensity score–matched subgroup, patients in the prone group had longer durations of ECMO than those in the control group (19 ± 14 d vs. 10 ± 8 d, respectively; P = 0.03) but lower rates of hospital mortality (30% vs. 53%, respectively; P = 0.02).

The authors are to be congratulated for this well-conducted retrospective analysis. These data represent an important addition to the current body of observational data (Table 1) suggesting that PP of venovenous ECMO–supported patients is feasible and safe and may have physiologic and potential survival benefits. However, several limitations of this study need to be appreciated. As noted by the authors, the retrospective nature of the study, small sample size, lack of randomization, and center-level variations in practice may all affect further interpretation. More patients in the control group died of multiple organ failure (71% vs. 54%) and fewer from irreversible lung damage (10% vs. 26%).

Although the magnitude of treatment effect (absolute risk reduction of 23%) seen with PP in this study may not be reproducible in larger studies, it should be noted that there is a sound pathophysiologic rationale for this practice. Most observational studies in the past have reported similar physiologic benefits, with some reporting improved survival (Table 1). Franchineau and colleagues (12) used electric impedance tomography to describe the impact of PP on global and regional ventilation and to define optimal positive end-expiratory pressure in patients receiving venovenous ECMO. There was progressive redistribution of tidal volumes and end-expiratory lung impedance from ventral to dorsal regions with improvements seen in static lung compliance. Guervilly and colleagues (13) reported a 90-day mortality of 62% in patients who were managed in the supine position.

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Supported by Metro North Hospital and Health Service (K.S.).

DOI: 10.1513/AnnalsATS.202011-1444ED

Editorials
Table 1. Summary of studies reporting prone positioning of patients during venovenous ECMO

| Author | Country | Sample Size (n) | PP on ECMO | Supine ECMO | Mortality Definition | PaO2:FIO2 Prior to PP* | Details of PP |
|--------|---------|-----------------|------------|-------------|---------------------|----------------------|--------------|
|        |         |                 | Patients (n) | Mortality [n (%)] | Duration (d)* | Patients (n) | Mortality [n (%)] | Duration (d)* |
| Guervilly | 2019 (13) | France | 168 | 91 (55) | 20 (16) | 77 | 29 (62) | 9 (8) |
|         | 100† | | 50 | 18 (36) | 20 (16) | 50 | 29 (58) | 9 (9) |
|         |         | | Definition: Trigger: persistent hypoxemia (n = 30), failure to wean ECMO after 10 d and lung consolidations on chest X-ray or lung ultrasound (n = 11), physician discretion (n = 50); time to first PP session, 5 ± 4 d; average 3 (range 1–7) PP sessions per patient; 12–16 h/session |
| Garcia | 2020 (16) | France | 25‡ | 14 | 11 (78) | 10 (24) | 11 | 3 (27) | 7 (7) |
|         |         | | Definition: Trigger: persistent hypoxemia on ECMO; time to first PP session, 1.5 d; minimum 1 PP session/session; 16 ± 1.6 h/session |
| Rilinger | 2020 (15) | Germany | 158 | 38 | 24 (63) | 12 (8) | 120 | 76 (63) | 6 (5) |
|         |         | Hospital | 81 | 51 (63) | 6 (5) | |
| Giani | 2021 (11) | Italy | 240 | 107 | 36 (34) | 19 (14) | 133 | 61 (50) | 11 (9) |
|         | 132‡ | | 66 | 20 (30) | 19 (14) | 66 | 31 (53) | 10 (8) |
|         |         | Hospital | 73 | 50 (50) | 15 (11) | |

Definition of abbreviations: ECMO = extracorporeal membrane oxygenation; PaO2:FIO2 = ratio of arterial oxygen partial pressure to fractional inspired oxygen; PP = prone positioning.

*Mean ± standard deviation.
†Analysis of matched patients.
‡Patients with coronavirus disease (COVID-19)–related acute respiratory distress syndrome.

Only studies that report data from a comparator group are included.
with the use of electric impedance tomography, biomarkers, or respiratory mechanics and applying novel trial designs, such as Bayesian techniques, should be considered to overcome the challenges of a randomized trial in this population.

Many questions remain for such a trial design. It remains unclear, for instance, when PP should be initiated and for how long it should be performed. There is observational data to suggest early and prolonged PP may be beneficial (15). Standardizing mechanical ventilation and ECMO weaning procedures will be critical in such a trial. Time to successful liberation from the combination of invasive mechanical ventilation and ECMO is an important additional endpoint for future studies, together with disability-free survival. Clinical trials are expected to shed light on these questions in the coming years (NCT04139733 and NCT04607551). The role of PP during venovenous ECMO appears promising, yet widespread, routine adoption of the technique should await more rigorous evidence.

Author disclosures are available with the text of this article at www.atsjournals.org.

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