Efficacy of proning in acute respiratory distress syndrome on extracorporeal membrane oxygenation

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ABSTRACT

Objectives: Proning patients with acute respiratory distress syndrome (ARDS) has been associated with increased survival, although few data exist evaluating the safety and feasibility of proning patients with ARDS on extracorporeal membrane oxygenation (ECMO).

Methods: A single-institution retrospective review of all patients with ARDS placed on ECMO between March 1 and May 31, 2020, was performed. All proning events were evaluated for complications, as well as change in compliance, sweep, oxygenation, and flow. The primary outcome of this study was the rate major morbidity associated with proning while on ECMO.

Results: In total, 30 patients were placed on ECMO for ARDS, with 12 patients (40%) proned while on ECMO. A total of 83 proning episodes occurred, with a median of 7 per patient (interquartile range, 3-9). No ECMO cannula-associated bleeding, cannula displacement, or endotracheal tube dislodgements occurred (0%). Oropharyngeal bleeding occurred twice (50%). Four patients were proned with chest tubes in place, and none had complications (0%). Lung compliance improved after proning in 70 events (84%), from a mean of 15.4 mL/mm Hg pre-proning to 20.6 mL/mm Hg post-proning (P < .0001). Sweep requirement decreased in 36 events (43%). Oxygenation improved in 63 events (76%), from a mean partial pressure of oxygen of 86 pre-proning to 103 post-proning (P < .0001). Mean ECMO flow was unchanged.

Conclusions: Proning in patients with ARDS on ECMO is safe with an associated improvement in lung mechanics. With careful planning and coordination, these data support the practice of proning patients with severe ARDS on ECMO.

CENTRAL MESSAGE

Proning in patients with ARDS on ECMO is safe and shows improvement in lung mechanics. With planning and coordination, these data support the practice of proning patients with severe ARDS on ECMO.

PERSPECTIVE

A large number of patients were proned at a single institution for ARDS. Which patients would benefit from proning remains to be determined. However, if the primary barriers to offering proning are lack of experience and concerns regarding safety, then, once those hurdles have been overcome, the possibility will exist to expand to trials and further investigations that may answer those questions.

Prone positioning of patients with severe acute respiratory distress syndrome (ARDS) has been associated with improved survival.1 The physiologic effects of proning are improved oxygenation,2 decreased ventilator-associated lung injury,3,4 and improved compliance.5,6 While the benefits in ARDS have been demonstrated, the efficacy and safety of proning patients with severe ARDS requiring venovenous (VV) extracorporeal membrane oxygenation (ECMO) remains unknown.
Recently, with the coronavirus disease-19 (COVID-19) pandemic, the rate of ARDS has increased significantly in the past year. In patients with COVID-19 ARDS, patients who were on mechanical ventilation had improved oxygenation when proned. However, many patients with COVID-19 had severe ARDS that required VV-ECMO support, with current data demonstrating poor overall survival of 40% to 60% in this subset. This increased demand for ECMO during the COVID-19 pandemic highlighted the need to further define the role of proning while on ECMO.

Given the lack of data regarding the role and safety of proning patient on ECMO, our institution selectively proned patients with COVID-19 who were cannulated for ECMO. In this study, we will describe the patient population that was proned, evaluate pulmonary mechanics with resultant changes in ECMO settings, and report the safety of proning while on ECMO support.

METHODS

Patient Population

We conducted a retrospective analysis of all patients admitted to New York University Langone Health (NYULH) Manhattan with severe ARDS requiring initiation of ECMO support between March 1 and May 31, 2020. All patients placed on ECMO for severe ARDS during this time had ARDS secondary to COVID-19. COVID-19 was diagnosed by nasal pharyngeal swab for reverse transcriptase polymerase chain reaction assay in all patients. All patients were placed on VV-ECMO. The NYULH institutional review board approved this human subjects study (no.: i20-00611) on April 24, 2020, and data were collected from direct chart review.

Patient Selection and Proning

Patients on ECMO for ARDS were evaluated for proning by the critical care physician and a cardiothoracic surgeon. Criteria for proning while on ECMO were clinically based on little to no improvement in ECMO requirements after 10 days, with no defined compliance cutoff or ratio of arterial oxygen partial pressure to fractional inspired oxygen (P/F) ratio threshold used. The time point of 10 days was used, as it was the observed median duration of ECMO during the pandemic. Retrospective data show the median was 11 days for the entire cohort. The decision to prone was determined by the inability to wean sweep requirement, inability to decrease ECMO flows, decrease in compliance on the ventilator, and improvement on radiographs of the chest. Body mass index, chest tubes, and difficult airway were not considered in the selection criteria. There were no exclusion criteria. In summary, patients were considered for proning if they fell into one of the following cohorts: (1) patients had increased sweep requirement, and worsening compliance; and (2) patients had no clinical improvement after 2 weeks, determined by inability to decrease sweep, decreased ECMO flow, continued low compliance, or no improvement on serial radiographs of the chest. For patients with prolonged ECMO courses, multiple episodes of proning were used when the aforementioned criteria were met.

A team consisting of an anesthesiologist, intensive care, advanced care practitioner, bedside nurse, perfusionist, and respiratory therapist was present when patients were prone or placed supine. Patients were manually proned or supinated, and no proning beds were used. ECMO cannulas were secured to the skin with multiple silk sutures along the length of the cannula. The internal jugular (IJ) cannula was also secured with a Velcro headband, and all ECMO cannula connections were reinforced with plastic zip ties. Tracheostomy tubes were secured with a foam and Velcro tracheostomy collar, and tracheostomy tubes were not routinely sutured. Chest drains (if present) were secured with silk sutures and occlusive dressings.

In patients with an endotracheal tube, the head was rotated to the side, facing the ventilator to allow for the tube to exit without kinking. In patients with a tracheostomy, the head and chest were supported in the prone position with pillows to allow for a neutral neck position with no pressure on the tracheostomy tube or appliance. All patients were paralyzed during the time of turning the patient prone or supine. Patients were kept prone between 12 and 18 hours.

Pulmonary Mechanics and ECMO Circuit Measurements

All patients were intubated before cannulation for ECMO, with a median of 2 days (interquartile range [IQR], 1–4). Selection criteria are P/F ratio less than 150 mm Hg or a pH less than 7.25 with an arterial partial pressure of carbon dioxide (pCO2) greater than 60 mm Hg. Once patients were cannulated for ECMO, ventilation was managed with a lung-protective strategy using pressure control ventilation with a target peak inspiratory pressure of less than 25 mm Hg, positive end-expiratory pressure (PEEP) of 10 to 14 mm Hg, respiratory rate of 16 breaths/min or fewer, and fraction of inspired oxygen of 0.40 or less.

Static pulmonary compliance was calculated using tidal volume, plateau pressure, and PEEP.

\[
\text{Compliance} = \frac{\text{Tidal Volume (mL)}}{\text{Plateau pressure} - \text{PEEP (mmHg)}}
\]

The difference in compliance was calculated using the difference between postproning and preproning compliance while patients were in supine position.

Oxygenation was evaluated using the arterial partial pressure of oxygen (pO2), determined from blood gases drawn from radial arterial lines. The difference in oxygenation was calculated using the difference between postproning and preproning pO2 ratio while patients were in the supine position. The fraction of delivered oxygen for the ECMO circuit was kept at 0.45 for all patients. ECMO circuit measurements were all collected while the patients were in the supine position before proning and after being supinated again. Sweep and ECMO circuit flow were measured, as they affect CO2 clearance and oxygenation, respectively. ECMO circuit flow was titrated to oxygenation needs but did not exceed revolutions per minute thresholds for possible hemolysis. Sweep was titrated for a goal pCO2 ≤45 mm Hg.

Measurements of pulmonary mechanics and oxygenation, as well as
ECMO settings, were noted after paralysis for proning was initiated and shortly after returning to the supine position.

**Anticoagulation**
Therapeutic anticoagulation with an intravenous heparin infusion was initiated on every patient with a goal anti-factor Xa level exceeding 0.15 IU/mL and a partial thromboplastin time of less than 70 seconds.\(^8\)

**Outcomes**
The primary outcome for this study was the rate of major morbidity associated with proning while on ECMO. Major morbidity was defined as dislodged ECMO cannula, airway, chest tube, or invasive lines, as well as bleeding from the cannulation site. A secondary objective was to evaluate whether proning resulted in improved compliance, sweep requirement, or oxygenation. Additional morbidity associated with proning including tracheostomy and endotracheal tube complications, and skin breakdown or lacerations were also noted.

**Statistics**
Data analysis and statistics were performed with GraphPad Prism. Descriptive statistics of continuous variables were reported as mean ± standard deviation. Student t-tests were used to compare normally distributed continuous data. Nonparametric variables were reported as median with IQR. Two unpaired variables were evaluated with Mann–Whitney U tests.

**RESULTS**

**Proned Patients on ECMO**
From March 1, 2020, to May 31, 2020, 30 patients with ARDS were placed on ECMO at the NYULH Manhattan campus. All 30 patients had ARDS secondary to COVID-19, and all were placed on VV-ECMO (Table 1). Before cannulation for VV-ECMO, 22 (73\%) patients were proned. Of the 30 patients on VV-ECMO, 12 (40\%) patients were proned while on VV-ECMO. Venous access for cannula configuration used was the right IJ for the drainage cannula and right femoral vein for the return cannula\(^8\) as the primary strategy. In 28 patients (94\%), a 21-French cannula was used for the right IJ return limb and a 25-French cannula was used for right femoral vein drainage. One patient (3\%) had a history of hemodialysis and kidney transplant with an occluded right IJ, so the return cannula was placed in the left femoral vein. In 1 patient (3\%), the wire was unable to be placed in the right femoral vein, so the drainage cannula was placed in the left femoral vein. The 1 patient with a drainage cannula in the left femoral vein had aberrant anatomy, with poor drainage requiring an intraoperative change to a right femoral drainage cannula. No other patients required changes to cannulation for drainage. No patients were converted to venoarterial ECMO.

A total of 83 proning episodes were performed, with a median of 7 proning events per patient (IQR, 3-9). One patient was proned 24 hours after cannulation, with the median first proning episode 12 days (IQR, 9-13 days) after initiation of VV-ECMO. All 12 proned patients were successfully decannulated from VV-ECMO and weaned from mechanical ventilator support, with 11 (92\%) of the patients surviving to discharge (Table 2). The patients who were proned had a significantly longer ECMO duration (median 52 [IQR, 29-83] days vs 14 [IQR, 10-18] days, \(P<.0001\)), total ventilator duration (median 72 [IQR, 47-118] days vs 25 [IQR, 20-33] days, \(P<.0001\)), and hospital length of stay (median 45 [IQR, 25-62] days vs 20 [IQR, 12-30] days, \(P<.0001\)).

**TABLE 1. All patients cannulated for ECMO: Characteristics and outcomes**

| Variables                              | All patients on ECMO (n = 30) |
|----------------------------------------|--------------------------------|
| Sex, no. (%)                           |                                |
| Male                                   | 26 (87)                        |
| Female                                 | 4 (13)                         |
| Age, y, median (IQR)                   | 41 (32-47)                     |
| BMI, kg/m\(^2\), median (IQR)          | 32 (29-36)                     |
| ECMO duration, d, median (IQR)         | 19 (12-40)                     |
| Total ventilator duration, d, median (IQR) | 34 (25-62)                 |
| Days of ventilator dependence after ECMO decannulation, median (IQR) | 11 (6-16) |
| Hospital length of stay, d, median (IQR) | 45 (30-74)                  |
| Outcome, no. (%)                       |                                |
| Survived ECMO                          | 28 (93)                        |
| Survived to discharge                  | 27 (90)                        |

**TABLE 2. Change in compliance from proning while on ECMO**

| Variables                              | Proned ECMO (n = 12) | Not proned ECMO (n = 18) | P value |
|----------------------------------------|----------------------|--------------------------|---------|
| Sex, no. (%)                           |                      |                          |         |
| Male                                   | 11 (92)              | 15 (83)                  |         |
| Female                                 | 1 (8)                | 3 (17)                   |         |
| Age, y, median (IQR)                   | 42 (37-26)           | 39 (29-48)               | .71     |
| BMI, kg/m\(^2\), median (IQR)          | 30 (27-38)           | 33 (29-35)               | .68     |
| ECMO duration, d, median (IQR)         | 52 (29-83)           | 14 (10-18)               | <.0001  |
| Total ventilator duration, d, median (IQR) | 72 (47-118)         | 25 (20-33)               | <.0001  |
| Days of ventilator dependence after ECMO decannulation, median (IQR) | 18 (14-30) | 7 (5-10) | <.0001 |
| Hospital length of stay, d, median (IQR) | 91 (63-159)          | 34 (24-44)               | <.0001  |

**Outcome, no. (%)**

| Survived from ECMO                     | 12 (100)             | 16 (89)                  |         |
| Survived to discharge                  | 11 (92)              | 16 (89)                  |         |

ECMO, Extracorporeal membrane oxygenation; IQR, interquartile range; BMI, body mass index (weight in kilograms divided by the square of the height in meters).
days, prone vs nonprone respectively, \( P < .0001 \), days of ventilator dependence after ECMO decannulation (median 18 [IQR, 14-30] days vs 7 [IQR, 5-10] days, prone vs non-prone, respectively, \( P < .0001 \)), and hospital length of stay (median 91 [IQR, 63-159] days vs 34 [IQR, 24-22] days, prone vs nonprone respectively, \( P < .0001 \)) compared with the group of patients with ECMO who were not proned.

### Proning Complications

During all 83 proning events, no (0%) ECMO cannulas were dislodged and no (0%) bleeding from the cannulation sites occurred (Figure 1). Four of the 12 patients (33%) had chest tubes while being proned on VV-ECMO. A total of 19 proning events occurred with chest tubes in place. Of those 19, no (0%) chest tubes were dislodged and no (0%) bleeding complications around the chest tube sites were noted. No invasive lines (0%) were dislodged during any proning events, and no bleeding complications (0%) around the invasive lines were noted. No recirculation events were associated with proning.

Two of the 12 patients (17%) had endotracheal tubes when proned, with a total of 4 episodes of proning (5%). Each patient had one episode of mucosal lacerations leading to bleeding (50%), although no (0%) endotracheal tubes were dislodged. Oropharyngeal bleeding was managed with packing of the oropharynx with blood transfusion requirement in one patient. No cases required surgical intervention. The remaining 10 patients (83%) had a tracheostomy. Of the 79 proning events with tracheostomies (95%), one (1%) had a cracked flange, with no (0%) dislodgement and no (0%) bleeding from the airway around the time of proning (Figure 1).

Despite the good outcomes from the defined primary outcomes, 1 patient had a complication of a pressure sore on his chest after his third proning episode. The remainder of the patients did not have any issues with skin breakdown from proning. No change in hemodynamic stability were noted between proning and supine position.

### Compliance and Sweep Requirement

Compliance improved after proning in 70 (82%) of the proning events, with a mean compliance improvement of 65%. Compliance improved from 15.4 ± 6.52 mL/mm Hg to 20.65 ± 8.41 mL/mm Hg, \( P < .0001 \) (Figure 2). A greater than 10% improvement in compliance was present in 61 proning events, which is 74% of all proning episodes and 88% of all proning events where compliance improved. The number of events with improved compliance is present in Table E1.

Sweep requirement decreased after 36 proning events (43%), with a mean 5% decrease in sweep after proning. Sweep requirement decreased from a mean of 6.5 ± 2.16 L/min to 6.1 ± 2.03 L/min, \( P < .01 \) (Figure 3). Improved compliance correlated with decreased sweep in 27 proning events.

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**FIGURE 1.** Proning complications. Flowchart indicates the number of patients during the time period who were cannulated for ECMO for acute respiratory distress syndrome, the number of those patients who were proned, and the incidence of complications related to the airway, ECMO cannulas, and chest tubes. VV, Venovenous; ECMO, extracorporeal membrane oxygenation.
**Oxygenation and ECMO Flow**

Oxygenation measured by pO₂, improved after proning 66 times (80%), with a mean pO₂ increase of 21%. The pO₂ was 86 ± 20 preproning and 103 ± 33 postpronning, $P < .0001$ (Figure 4). A greater than 10% improvement in pO₂ was present in 48 proning events, which is 58% of all proning episodes and 73% of all prones where oxygenation improved. The number of events with improved oxygenation is reported in Table E1.

ECMO circuit flow was unchanged or had less than a 10% change in 68 prones (82%), with a mean decrease of 2%. The mean preprone ECMO flow was 4.06 ± 0.72 L/min, compared with a mean postprone ECMO flow of 3.98 ± 0.72 L/min, $P = .08$ (Figure 5).

**DISCUSSION**

Prone positioning has been considered a standard part of ARDS management for some time.¹ The COVID-19 pandemic and its devastating impact has renewed interest in the effects of prone positioning on this specific etiology of ARDS.⁷ Likewise, in some situations, patients with severe forms of ARDS may be supported with VV-ECMO. While there may be potential benefit to adding prone positioning to VV-ECMO support, it is rarely employed.
Proning in ECMO is associated with:

- NO dislodged tubes, lines, or cannulas
- NO bleeding from chest tubes, lines, or cannulas
- 50% bleeding with endotracheal tubes

**Ventilation**
- Improved compliance
- Decreased sweep

**Oxygenation**
- Improved oxygenation
- Stable ECMO flow

**FIGURE 6.** Chart demonstrates outcomes from proning during ECMO. ECMO, Extracorporeal membrane oxygenation.

Possible explanations for poor uptake of prone positioning with VV-ECMO include concerns regarding safety, a lack of experience, and an unclear benefit to the patient.

In this retrospective review, proning was found to be associated with minimal complications, as well as improved pulmonary mechanics, in patients cannulated for ECMO. In 12 patients with multiple proning episodes per patient, no cannulas, chest tubes, invasive lines, or tracheostomies were dislodged or had bleeding requiring intervention. However, we did note a 50% oropharyngeal bleeding rate in patients who had endotracheal tubes associated with proning. The 2 patients with endotracheal tubes were the first 2 patients who were prone while cannulated for ECMO during the COVID-19 surge, and both had significant oropharyngeal bleeding requiring packing, with 1 patient requiring blood transfusion. It is interesting that the only complications in our series was associated with endotracheal tubes, as many providers are hesitant to prone patients with tracheostomies due to the logistic difficulty of supporting the patient without torqueing or putting pressure on the tracheostomy. Given the prolonged ventilatory requirement for patients requiring proning while on VV-ECMO, the authors recommend early tracheostomy before proning to limit risk of oropharyngeal bleeding. Otherwise, if proning with an endotracheal tube is necessary, extra attention should be paid to padding around the endotracheal tube. There are limited studies evaluating the safety of turning and the prone position for this subset of patients, although a systematic review found low rates of complication with no dislodges cannulas, chest tubes or airways.

Of the 7 included studies, one demonstrated a 15% rate of bleeding from ECMO cannula sites and a 14% rate of chest tube bleeding. One reason for the difference in bleeding from cannulation sites may relate to dedicated use of a proning team, which centralized the expertise in this area, allowing, as well as all patients paralyzed during the time of turning.

Proning was also associated with improved compliance and improved oxygenation (Figure 6). Our series demonstrated a mean improvement in P/F ratio of 68%, with a majority of patients showing improvement. Of the 70 proning events with increased compliance, there was an associated clinical improvement with decreased sweep requirement in 27 of those events (39%). Reduced sweep gas requirement on ECMO after proning may indicate improved gas exchange (particularly in pCO₂); however, several issues may confound the validity of this finding. First, sweep is titrated according to pCO₂ (generally to pCO₂ <45 mm Hg), and different providers may have different thresholds for adjusting sweep on the ECMO circuit. Second, with prolonged ECMO support, issues of oxygenator membrane efficiency become important and, in fact, several patients had circuit changes that affected the sweep requirement.

Proning also led to an increased P/F ratio in 68% of events in patients with COVID-19 who were cannulated for ECMO, which is similar to data for other series evaluating the effect of proning for intubated patients with COVID-19. This improvement in oxygenation was not attributable to any changes in ECMO flow, as the flow decreased or had minimal change in 82% of the events, with a mean decrease of 2% in ECMO flow.

While this analysis demonstrates both the safety and feasibility of proning patients cannulated for ECMO, with improved compliance and oxygenation in a majority of patients, we were unable to determine whether proning was associated with improved outcomes. The patients who were proned and those who were not both had good survival to decannulation (100% and 89%, respectively) and good survival to discharge (92% and 89%, respectively). However, this study points to 2 phenotypes of COVID-19 ARDS leading to ECMO requirement. The patients who were in the proned group were found to have significantly longer ECMO duration (52 vs 14 days, \( P < .0001 \)), ventilator duration (72 vs 25 days, \( P < .0001 \)), ventilator days after ECMO decannulation (18 vs 7 days, \( P < .0001 \)), and hospital length of stay (91 vs 34 days, \( P < .0001 \)). Given that patients were proned due to minimal or no improvement in ECMO requirement after 2 weeks, proning was not the primary variable that led to these differences, but rather was a secondary event after patients had clinically proven to be in the group requiring prolonged support. There was no significant difference in patient age, sex, body mass index, or preexisting conditions between the 2 groups, and the underlying cause for the different clinical
courses is unknown. However, it is notable that the patients who were proned, despite significantly prolonged ECMO and ventilator support, had similar outcomes to the nonproned cohort. The good outcome of 90% survival to discharge (for the entire cohort) is contrary to one small single institution retrospective research letter showed a 79% 28-day mortality compared with the control ECMO group, with a 27% 28-day mortality. The differences between the reported data are likely due to multiple factors, but our series demonstrates that proning patients cannulated for ECMO is not necessarily associated with worse survival, as suggested by other data.

This study is notable for having a large number of pruning events in patients cannulated for ECMO secondary to COVID-19, as well as demonstrating that compliance and sweep requirement can improve with pruning. However, limitations include the fact that it was a single-institution study with a small cohort, retrospective in nature, and unable to determine if there was any survival benefit associated with pruning. Which specific patients would benefit from proning remains to be determined. It seems unlikely that all patients require proning, given that some patients clearly recovered and weaned from ECMO without it. However, if the primary barriers to offering proning are lack of experience and concerns regarding safety, then, once those hurdles have been overcome, the possibility will exist to expand to clinical trials and further investigations that may answer those questions.

Conflicts of Interest Statement
Zachary N. Kon reported consultant for Medtronic, Inc, and Breethe, Inc. Aubrey C. Galloway reported IP and royalties from Medtronic, Inc, and Edwards Lifesciences. Nader Moazami reported advisory board for Medtronic, Inc. All other authors reported no conflicts of interest.

The Journal policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: EMCO, proning
TABLE E1. Number and percentage of events with improved compliance and P/F

| Patient no. | Times prone | No. events with improved compliance | % events improvement compliance | No. events with improved P/F | % events improvement P/F |
|-------------|-------------|-------------------------------------|--------------------------------|-----------------------------|--------------------------|
| 1           | 2           | 2                                   | 100%                           | 1                           | 50%                      |
| 2           | 2           | 2                                   | 100%                           | 1                           | 50%                      |
| 3           | 3           | 3                                   | 100%                           | 3                           | 100%                     |
| 4           | 12          | 9                                   | 75%                            | 10                          | 83%                      |
| 5           | 12          | 10                                  | 83%                            | 10                          | 83%                      |
| 6           | 6           | 5                                   | 83%                            | 5                           | 83%                      |
| 7           | 6           | 5                                   | 83%                            | 5                           | 83%                      |
| 8           | 8           | 8                                   | 100%                           | 6                           | 75%                      |
| 9           | 3           | 1                                   | 33%                            | 3                           | 100%                     |
| 10          | 8           | 8                                   | 100%                           | 5                           | 63%                      |
| 11          | 8           | 7                                   | 88%                            | 5                           | 63%                      |
| 12          | 13          | 9                                   | 69%                            | 9                           | 69%                      |

P/F, Ratio of arterial oxygen partial pressure to fractional inspired oxygen.