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Community Experience With Acute Respiratory Distress Syndrome in the Prone Position

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Objectives: Mechanical ventilation in the prone position has been shown to improve outcomes in randomized trials of patients with moderate to severe acute respiratory distress syndrome and is recommended in clinical practice guidelines. However, data is lacking on the results of attempts to implement this practice in the community outside of clinical trials. To describe our early outcomes implementing mechanical ventilation in the prone position.

Design: Retrospective cohort study.

Setting: Medical intensive care unit of a large community-based teaching hospital.

Participants: All patients ventilated in the prone position between June 2013 and October 2016.

Measurements and Main Results: We describe patient characteristics, mortality, and frequency of complications (such as skin breakdown and accidental extubation) at our center. Eighty-one patients with a mean age of 55 years underwent mechanical ventilation in the prone position during the study period. Most patients also received vasopressors, neuromuscular blockade, and steroids. Overall mortality was 43%. The duration of the first proning session ranged from 1.5 to 40.5 hours. Mortality was lower (34%) in those ventilated in the prone position for more than 16 hours during the first session. In the 50 patients without treatment limitations, only 14% expired. There were no accidental extubations during prone positioning. Most of those who died had limitations placed on treatment prior to death.

Conclusions: Overall mortality was higher in our cohort than in the randomized trial. However, differences such as lack of stabilization period, different cultures impacting end-of-life decisions, and timing of enrollment in the course of illness limit interpretation of this comparison. This exercise allows identification of areas for future quality improvement efforts such as increasing the duration of some proning sessions. Complications of prone positioning were uncommon.

Key Words: acute respiratory distress syndrome; intensive care unit; mechanical ventilation; outcomes; prone positioning

Acute respiratory distress syndrome (ARDS) is a heterogeneous disorder affecting 10% of ICU patients (1). The Berlin definition of ARDS classified severity based on Pao_2 to Fio_2 ratios into three categories: mild, moderate, and severe. These correspond to mortality rates of 27%, 32%, and 45%, respectively (2).

Low tidal volume ventilation, prone positioning, and neuromuscular blockade have been reported to improve mortality in clinical trials of ARDS (3–5), although the benefits of neuromuscular blockade were not seen in recent multicenter trial (6). All of these interventions are recommended in clinical practice guidelines (7). However, implementation of these interventions outside trial settings presents challenges which may impact their effectiveness in the community. Failure to implement low tidal volume ventilation in clinical practice was documented repeatedly in multiple studies for many years following publication of evidence of its effectiveness (8, 9).

Ventilation in the prone position was shown in a randomized controlled trial (Proning Severe Acute Respiratory Distress Patients [PROSEVA] trial) of moderate to severe ARDS in French ICUs with

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greater than 5 years' experience using this technique to reduce mortality from 32% in the supine position group to 16% in the prone position group (5). After publication of this trial, we began to implement mechanical ventilation in the prone position for ARDS in our ICU in patients similar to those shown to benefit in this trial.

We sought to describe our early outcomes from this quality improvement project and determine how our early experience compared with the result of the PROSEVA trial patients in the prone group.

MATERIALS AND METHODS

Our institutional interprofessional clinical practice guideline for placing patients in prone position has been described previously (10). This guideline addressed indications for, and logistics of placing patient in prone position. Nurses and respiratory therapists practiced placing patients in prone position in a simulation environment. An institutional guideline on lung-protective ventilation for ARDS was also in place. However, actual treatment decisions were at the discretion of treating clinicians.

We then conducted a retrospective cohort study of patients who underwent mechanical ventilation in the prone position in our medical ICU between June of 2013 and October of 2016. Patients were identified by respiratory therapy charting. Patients in other ICUs, not meeting Berlin definition for ARDS, or who on chart review were found not to have undergone prone positioning were excluded.

Demographic and clinical data were abstracted from the electronic health record and entered into a Research Electronic Data Capture (REDCap) database (11). Collected clinical data included ICU admission diagnosis; cause of ARDS; comorbidities; use of vasopressors, inhaled nitric oxide, and dialysis; do-not-resuscitate (DNR) status; hospital mortality; physical therapy assessments; and complications such as skin wounds. DNR status means that there was an order in the electronic record instructing the nurses not to perform cardiopulmonary resuscitation in the event of cardiac arrest. In our institution, the decision to write this order is often accompanied by additional decisions to limit or withdraw aggressive ICU care, which would be separately documented in a note. However, for this project, only the DNR order was captured for analysis.

Descriptive statistics were used to characterize the cohort. Standardized differences were used to compare characteristics of PROSEVA patients in the prone group and Christiana Care patients. Continuous outcomes between Christiana Care patients and PROSEVA patients in the prone group were compared using unpaired *t* tests, while categorical outcomes were compared using *z* tests. Analysis was performed with SAS software (version 9.4, SAS Institute Inc., Cary, NC).

The study was approved by the Christiana Care Health System Institutional Review Board.

RESULTS

We identified 81 patients who underwent mechanical ventilation in the prone position in our medical ICU during the study period. The most common mode of ventilation was assist control volume control (56 patients) followed by assist control pressure control (22 patients). One patient underwent high frequency oscillatory ventilation, five patients received airway pressure release ventilation, and another five patients had more than one ventilator mode used. The median time between intubation and the first prone position session was 23.8 hours with a range from 2.1 hours to 411 hours (17 d). The duration of the first proning session in our cohort ranged from 1.5 to 40.5 hours with an average of 17.5 ± 7.9. The mean tidal volume among patient in assist control volume control was 5.8 mL/kg predicted body weight.

As shown in **Table 1**, on average the Christiana Care patients received lung-protective tidal volumes and a mean positive expiratory pressure of 14 centimeters of water. The mean Pao_2/Fio_2 was in the severe ARDS range at 99. More than half of the patients received steroids and neuromuscular blockade and the frequency of comorbid psychiatric disease was very high in these patients. The standardized difference calculations indicate that while some of the patients' characteristics between Christiana Care and PROSEVA are small (|Difference| < 0.2) such as Pao_2/Fio_2 ratio others are much larger such as sepsis (|Difference| > 1.3) (12).

As shown in **Table 2**, overall mortality was 43.2% and 19.6% of survivors required tracheostomy tube placement. Thirty-one patients in our cohort (37.8%) had a DNR order in place. Of these 31 patients, 28 died (90.3%). However, in the 50 patients without a treatment limitation order, only seven expired (14%). In addition, when we excluded patients in our cohort ventilated in the prone position for less than 16 hours, 53 patients remained with a mortality rate of 34%.

There were no accidental extubations during proning. Only three patients were identified as having skin wounds during their hospitalizations. All three patients had wounds on the sacrum/coccyx and one also had a wound at his tracheostomy site. Based on the locations of injury, these did not appear to be related to prone positioning. There were no endotracheal tube dislodgements. Eight patients had dislodgement of IV access including peripheral, central, and arterial lines. Thirteen patients were noted to have dependent edema of the eyes, lips, and tongue. We found that 38 out of 46 survivors (83%) of our patients were able to ambulate prior to discharge from the hospital.

DISCUSSION

Although guidelines and meta-analysis support the effectiveness of mechanical ventilation in the prone position for patients with moderate to severe ARDS, reports of outcomes from implementation of this practice outside of trials are rare (7, 13). To better understand our outcomes, we systematically compared our cohort of proned patients to the subset of PROSEVA trial patients randomized to prone positioning. As shown in Table 1, characteristics of our patients were similar to those in the PROSEVA trial. However, PROSEVA patients had higher prevalence of sepsis diagnosis (82.2% vs 12.3%) and lower prevalence of pneumonia (62.4% vs 74.1%). PROSEVA patients also had lower mean positive end-expiratory pressure (10 cm of water vs 14 cm of water) upon proning initiation. It seemed that neuromuscular blockade was used more frequently in PROSEVA study patients in the prone group (91.0% vs 85.2%) and steroids less frequently (39.6%

TABLE 1. Comparisons of Characteristics: Christiana Care Versus Proning in Severe Acute Respiratory Distress Syndrome Trial Patients

Characteristics	Christiana Care, *n* = 81	Proning in Severe Acute Respiratory Distress Syndrome Trial Patients, *n* = 237	Standardized Difference
Age, yr, mean ± SD	55 ± 15	58 ± 16	0.185
Comorbidities, *n* (%)			
Diabetes mellitus	14 (17.3)	50 (21.1)	0.095
Renal failure	9 (11.1)	10 (4.2)	−0.291
Liver disease	3 (3.7)	6 (2.5)	−0.071
Coronary artery disease	14 (17.3)	24 (10.1)	−0.221
Cancer	8 (9.9)	24 (10.1)	0.008
Chronic obstructive pulmonary disease	13 (16.1)	23 (9.7)	−0.200
Psychiatric disease/substance abuse	30 (37.0)		
ICU characteristics			
Sepsis, *n* (%)	10 (12.3)	194 (82.2)	1.459
Pneumonia, *n* (%)	60 (74.1)	148 (62.4)	−0.244
Body mass index, mean ± SD	31 ± 9	28 ± 6	−0.401
Vasopressor use, *n* (%)	54 (66.7)	172 (72.6)	0.130
Neuromuscular blockade, *n* (%)	69 (85.2)	212 (91.0)	0.189
Renal replacement therapy, *n* (%)	20 (24.7)	27 (11.4)	−0.375
Steroids, *n* (%)	52 (64.2)	91 (39.6)	−0.494
Ventilator data			
Tidal volume, mean ± SD	354 ± 74	384 ± 63	0.453
Tidal volume, mg/kg predicted body weight		6.1 ± 0.6	
Male	5.6 ± 0.8		
Female	6.0 ± 0.9		
Rate, mean ± SD	31 ± 8	27 ± 5	−0.645
Positive end-expiratory pressure, cm H_2O, mean ± SD	14 ± 3	10 ± 3	−1.433
Fraction of inspired oxygen, mean ± SD	0.86 ± 0.15	0.79 ± 0.16	−0.444
Plateau pressure, cm H_2O, mean ± SD	27 ± 5	24 ± 5	−0.669
Pao_2/Fio_2 ratio, mean ± SD	99 ± 42	100 ± 30	0.021

Prone Positioning in Severe Acute Respiratory Distress Syndrome (5) was a randomized trial with a prone and supine group. Here we compare to prone group only.

vs 64.2%). Interestingly, as many as 37% of our cohort had comorbid psychiatric disease or substance abuse. The frequency of these comorbidities was not reported in the PROSEVA trial.

Overall mortality was lower in the PROSEVA study prone group patients than in our cohort (16.0% vs 43.2%), however, after excluding patients with a DNR order, the mortality of our cohort (13.7%) was very similar to that of the PROSEVA patients. This raises the question about which patient factors need to be accounted for when looking at ARDS mortality rates in the medical literature.

The average duration of the first proning session in our cohort was 17.5 ± 7.9, which is similar to the average duration of 17 hours per day in the PROSEVA trial. As shown in Table 2, among survivors, time to extubation and length of stay were shorter in our cohort.

Although many characteristics of both patient populations were similar, there are several important differences. First, the PROSEVA trial had a 12–24 hour stabilization period prior to randomization and only included patients within 36 hours of ARDS diagnosis (5). In contrast, we included all patients who underwent mechanical ventilation in the prone position during the study period regardless of the ARDS duration (including one patient who was placed in the prone position after 17 d of mechanical ventilation), and without any stabilization period. Additionally, we

TABLE 2. Outcomes of Christiana Care Versus Proning in Severe Acute Respiratory Distress Syndrome Trial Patients

Outcomes	Christiana Care	Proning in Severe Acute Respiratory Distress Syndrome Trial Patients	*p*
Mortality @ 28 d, *n* (%)	35 (43.2)	38 (16.0)	< 0.001
Successful extubation among survivors, *n* (%)	37 (80.4)	186 (93.5)	0.005
Time to extubation (d ± SD)			
Survivors	12 ± 11	17 ± 16	0.063
Nonsurvivors	10 ± 10	18 ± 14	0.001
Length of ICU stay (d ± SD)			
Survivors	14 ± 10	24 ± 22	0.004
Nonsurvivors	10 ± 10	21 ± 20	0.002
Complications			
Cardiac arrests, *n* (%)	3 (3.7)	16 (6.8)	0.318
Ventilator-associated pneumonia, *n* (%)	0 (0)	52 (22.8)	< 0.001
Ambulatory distance (feet ± SD)	84.1 ± 37	Not measured	

Prone Positioning in Severe Acute Respiratory Distress Syndrome (5) was a randomized trial with a prone and supine group. Here we compare to prone group only.

did not exclude patients who had treatment limitations, whereas these patients were excluded from the PROSEVA trial if such limitations were in place at the time of randomization (5).

The PROSEVA trial also excluded patients on home oxygen or chronic noninvasive ventilation, noninvasive ventilation for more than 24 hours prior to enrollment, and chronic disease with life expectancy less than 1 year; while our observational trial of patients actually treated with prone positioning included such patients (5). There also may be cultural differences in end-of-life care discussions between our institution in the United States and the European ICUs involved in the trial. The absence of ventilator-associated pneumonia diagnoses in our cohort compared with the 22.8% incidence in the PROSEVA study is almost certainly due to cultural and economic factors influencing definition of this syndrome in the United States versus Europe.

Although the above differences may explain why we could not achieve results similar to PROSEVA, our data suggest hypotheses for future work. For example, the large number of patients in our group whose first proning session was less than 16 hours represents a potential area for quality improvement efforts. The same is potentially true for patients who were not placed in the prone position for many days after intubation. Unfortunately, we did not record the reason for early termination of the first proning session or the time of ARDS diagnosis. The seemingly increased steroid use in our cohort combined with the higher mortality are interesting in the context of some research suggesting that steroids are beneficial in ARDS. Additionally, the higher frequency of pneumonia in our population raises the possibility that our cohort of ARDS patients may have had more pulmonary rather than nonpulmonary causes of ARDS, perhaps representing distinct phenotypes within this syndrome (14, 15). In addition to pulmonary and nonpulmonary etiologies of ARDS, multiple other approaches to phenotyping ARDS have been proposed (16). In addition to their often-discussed repercussions for clinical trials, further exploration of ARDS phenotypes have implications for future improvement science and quality improvement work.

It is encouraging that the majority of survivors in our population were able to ambulate prior to hospital discharge. This outcome was achieved despite the use of neuromuscular blockade and steroids in the majority of patients. It may reflect the young age of our patient population. The low incidence of complications from mechanical ventilation in the prone position also suggest that this intervention can be implemented safely.

Our study has several limitations. First, as a retrospective cohort study of only proned patients, we do not know how many patients who were candidates for prone positioning were not proned or why those decisions were made. It is also possible that the respiratory therapy documentation failed to capture some patients who were proned. Additionally, we do not know the details of goals of care discussions between the treating team and patients' family which likely had a significant impact on outcomes, particularly on mortality. Finally, our results may not be generalizable to other institutions or other types of ICUs.

In summary, overall mortality in our cohort was higher than that observed in the PROSEVA trial, but when excluding those with treatment limitation, the survival was similar. Although patient characteristics were comparable in both cohorts, differences between the populations related to timing of enrollment, end-of-life decision making, and clinical care may explain the differences. Despite this, we feel that examining prone positioning outcomes for ARDS patients in a community setting has value for planning future studies and quality improvement. Our study reflects the challenges of implementing in community settings recommendations from clinical trials, conducted in very controlled environments with highly selected patients. Future research to

determine optimal timing of prone initiation and how end-of-life decisions affect ARDS data would be of interest.

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