Identifying patient level factors of prone positioning therapy

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Abstract

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BACKGROUND: Acute Respiratory Distress Syndrome (ARDS) is an important cause of respiratory failure associated with high mortality and morbidity. Prone positioning (proning) is a proven therapy for ARDS and is strongly recommended by the American Thoracic Society guidelines. Despite this, it is vastly underutilized in eligible patients. We sought to determine the patient-level factors associated with proning in moderate-to-severe ARDS.

METHODS: We performed a secondary analysis of data collected as part of ROSE, a randomized controlled trial of patients with moderate-to-severe ARDS requiring intubation across 48 medical centers in the United States (U.S.). Patients who met criteria for moderate ARDS (PaO_2:$F_IO_2 \leq 150$ mmgHg) for less than 48 hours were included. We utilized data at baseline prior to enrollment, study day 1 – defined as the first day that patients met enrollment criteria – and study day 2. We excluded 31 patients who were already proned prior to the study period and one patient who was enrolled twice at two different sites. The outcome was proning during the initial 48 hours after moderate-to-severe ARDS diagnosis. The exposures of interest

included persistent hypoxemia after 24 hours, severe ARDS (PaO2/FiO2) ≤ 100 mmHg) , presence of pneumonia, baseline mean arterial pressure (MAP) ≤ 65 mm hg, need for renal replacement therapy within initial 48 hours, baseline plateau pressure (Pplat) and baseline cardiovascular Sequential Organ Failure Assessment (SOFA) score. Multivariable logistical regression was used to estimate odds ratios and related 95% confidence intervals.

RESULTS: Over 50% of the cohort were male and the median age was 56. Of the 974 patients, 13% of patients were proned in the first 48 hours after ARDS diagnosis. Proned patients were more likely to have pneumonia (86% vs. 76%), require renal replacement therapy (28% vs. 23%) and vasoactive agents on day 1 (72% vs. 66%) and were twice as likely to have persistent hypoxemia after 24 hours (28% vs. 14%). In multivariable analysis, pneumonia (OR 1.90, 95% CI 1.11-3.23), persistent hypoxemia after 24 hours (OR 2.32, 95% CI 1.45-3.71) and severe ARDS on initial diagnosis (OR 1.77, 95% CI 1.17-2.6) were significantly associated with proning. Markers of hemodynamic instability – hypotension and cardiovascular SOFA score – were not associated with proning.

CONCLUSIONS: Proning is more likely to be utilized in patients with pneumonia, persistent hypoxemia, and severe ARDS. Better understanding of the site-level and provider-level factors can inform rational decision-making in clinical care and improve the current low rates of proning.

Introduction

Acute Respiratory Distress Syndrome (ARDS) is a deadly clinical syndrome characterized by acute onset hypoxemia(PaO_2:FiO_2 ratio < 300) and bilateral pulmonary opacities not fully explained by cardiac failure or volume overload.[1] It is an important cause of acute respiratory failure associated with common conditions such as pneumonia, aspiration and sepsis.[1] ARDS is highly prevalent with an estimated occurrence of 10% in all intensive care unit (ICU) admissions and 24% among all mechanically ventilated patients.[2] Despite decades of dedicated research, it has an unacceptably high mortality of up to 40% with few beneficial therapies currently in practice.[3-8]

Prone positioning therapy (proning) - where a patient is placed face down- had long been demonstrated as a rescue therapy which improves oxygenation in ARDS.[9-18] In 2013, a multi-center randomized controlled trial (PROSEVA) demonstrated a 51% relative and 17% absolute reduction in mortality at 28 days in the prone group compared to the supine group in patients with moderate-to-severe ARDS, defined as the ratio of partial pressure of arterial oxygen to fractional inspired oxygen (PaO2/FiO2) ≤ 150 mmHg, with FiO_2 >60% and Positive End Expiratory Pressure (PEEP) ≥5 cm of water.[19] Subsequently, multi-society guidelines strongly recommended the use of early prone positioning to improve patient survival in severe ARDS.[20] Furthermore, the importance of developing implementation strategies for prone positioning in ARDS was reinforced by a 2017 policy statement on guidelines for treatment in ARDS.[20] Yet multiple epidemiologic studies demonstrated that proning was only utilized in 1/3 of eligible patients.[2, 21-23] There is a substantial knowledge gap as the factors that determine the implementation of prone positioning are unknown.[23]

This study seeks to understand the patient-level factors associated with the receipt of prone positioning therapy in moderate-severe ARDS in the United States (U.S.). Potential factors associated with higher utilization of proning could include persistent hypoxemia and pneumonia as a primary ARDS risk factor due to a higher likelihood of severe respiratory failure. Higher plateau pressures (Pplat) values could also be associated with worse ARDS and increased proning since Pplat is used as a surrogate for lung stress during mechanical ventilation and reducing Pplat is a mainstay of reducing lung stress in patients with ARDS.[8] On the other hand, markers of hemodynamic instability such as need for renal replacement therapy (RRT), hypotension, use of vasoactive medications and disease severity characterized by high Acute Physiology And Chronic Health Evaluation (APACHE) and Sequential Organ Failure Assessment (SOFA) scores could be associated with decreased proning. The findings of this study would be immensely helpful to understand the importance of patient level factors in proning and to inform future research efforts in increasing implementation of proning. Given the high mortality and morbidity of ARDS, it is imperative that we focus on understanding why we are underutilizing proven therapies such as proning.

Methods

Study design and setting:

The Prevention and Early Treatment of Acute Lung Injury (PETAL) Clinical Trials Network is a network of clinical centers funded by the National Heart, Lung and Blood Institute (NHLBI) to develop and conduct randomized controlled clinical trials. The objectives of the clinical trials were to prevent ARDS or provide early treatment to improve the outcomes of patients with ARDS. ROSE (the Reevaluation of Systemic Early Neuromuscular Blockade) was a multicenter randomized, controlled clinical trial conducted by PETAL from January 2016

through April 2018 to determine the efficacy and safety of early neuromuscular blockade (NMB) in patients with moderate-to-severe ARDS.[22] The study represented 48 academic and community medical centers across the U.S and enrolled 1006 patients. The PETAL central IRB provided oversight and the PETAL coordinating center gathered the data from each institution for ROSE. I conducted a retrospective cohort study using data from the ROSE study. The Institutional Review Board (IRB) of the Human Subjects Division of the University of Washington (UW) approved this study with waiver of informed consent.

Study population:

ROSE enrolled patients undergoing mechanical ventilation through an endotracheal tube who had the following criteria present for less than 48 hours: PaO_2:FIO_2< 150 mmHg with a PEEP ≥ 8 cm of water, bilateral pulmonary opacities on chest radiography or on computed tomography that could not be explained by effusions, pulmonary collapse, or nodules, and respiratory failure that could not be explained by cardiac failure or fluid overload.

The exclusion criteria included lack of informed consent, continuous NMB at enrollment, pregnancy, extracorporeal membrane oxygenation (ECMO) therapy, chronic respiratory failure with an outpatient PaCO2 >60 mmHg, home mechanical ventilation (non-invasive ventilation or via tracheotomy), body weight >1 kg/cm height, liver disease with Child-Pugh score of 12-15, bone marrow transplantation within the last 1 year, expected duration of mechanical ventilation <48 hours, withholding of life-sustaining treatment other than cardiopulmonary resuscitation (CPR), expected survival <24 hours, diffuse alveolar hemorrhage from vasculitis, burns >70% total body surface area (BSA), unwillingness to utilize low tidal ventilation , previous hypersensitivity or anaphylactic reaction to cisatracurium, NM conditions preventing safe use of a NM blockade agent, treatment for intracranial hypertension or other ARDS trial enrollment. I

excluded 31 patients who were proned prior to study onset. Additionally, one patient was enrolled twice in the study at two different sites and the latter enrollment was excluded from the study. There were 974 patients for final analysis after exclusions listed above.

Data collection and design:

Study day one was defined as the first day that patients met enrollment criteria. I utilized data from baseline, study day 1 and study day 2, similar to the PROSEVA trial which implemented early prone positioning within 48 hours of ARDS diagnosis.[19] Data was collected from the case report form (questionnaire) specifically designed and used in ROSE and the final data was shared in a secure file between the PETAL network and the University of Washington for this study.

Baseline demographic variables, ARDS risk factors, arterial blood gas (ABG) analysis, mechanical ventilator settings, respiratory parameters, Acute Physiologic Assessment and Chronic Health Evaluation (APACHE III) scores and Sequential Organ Failure Assessment (SOFA) scores were collected at enrollment and for the first 7 days after study enrollment.

Outcome and exposures:

The primary outcome was the receipt of prone positioning therapy within 48 hours of study onset. I considered individuals to have this outcome if it was recorded as "yes" to the prompt "proned on study day 1 or 2".

I defined persistent hypoxemia as a binary variable with the presence of at least moderate ARDS (PaO_2:$F_IO_2 \leq 150$ mmgHg) and FiO2 of ≥ 0.6 after 24 hours. Baseline PaO_2:F_IO_2 was coded as a binary variable based on severe ARDS (PaO_2:$F_IO_2 \leq 100$ mmHg). I evaluated markers of hemodynamic instability that could be associated with decreased proning including baseline mean arterial pressure (MAP) defined as either low (MAP $\leq$ 65 mm hg) or normal (MAP $\geq$65

mm Hg) and need for RRT which was defined as “yes” if RRT was initiated within initial 48 hours of ARDS diagnosis and “no” if it was initiated after 48 hours or never initiated. Other markers of disease severity included baseline SOFA scores which were measured in 5 organ systems (respiratory, cardiovascular, hematologic, gastrointestinal, and renal) with each organ scored from 0 to 4, resulting in an aggregated score ranging from 0 to 20, with higher scores indicating greater organ dysfunction and APACHE III scores which range from 0 to 299 with higher scores indicating more severe illness.

Statistical analysis:

Baseline characteristics were compared between patients who did or did not receive prone positioning therapy within 48 hours of ARDS onset. I computed descriptive statistics for all study variables using counts and proportions for categorical variables and mean (standard deviation) or median (interquartile range [IQR]) for continuous variables. Group differences were tested using two-tailed t-tests for means, chi-square tests for proportions and Mann-Whitney nonparametric test for medians as appropriate.

Multivariable logistic regression analyses were conducted to determine associations between respiratory and hemodynamic variables and the receipt of prone positioning at any time within 48 hours of ARDS onset, after adjustment for confounders. Model adjustment terms were fixed *a priori* and included BMI and baseline APACHE score. Questions assessing the use of RRT and baseline plateau pressure had significant missing-ness (67% and 47% respectively) and these covariates were thus excluded from the multivariate models. I considered a p-value of less than 0.05 as significant. All analyses were conducted using Stata (Version 16.0, College Station, TX).

Results

Out of a cohort of 974 mechanically ventilated adults with at least moderate ARDS (PaO_2:F_IO_2 ratio ≤150 mmHg), 128 patients (13%) received prone positioning therapy within 48 hours of ARDS diagnosis. Patient clinical characteristics by outcome (receiving prone positioning therapy) are shown in **Table 1**. Patients who received prone positioning therapy were more likely to have pneumonia as a primary or secondary cause of lung injury, receive renal replacement therapy and to be on vasoactive agents within the 48 hours after ARDS onset. Proned patients had more severe ARDS on onset with a PaO_2:F_IO_2 <100 mmHg and were twice as likely to have persistent hypoxemia with a PaO_2:F_IO_2 <150 mmHg and requiring a FiO2 of at least 0.6. Age, BMI, patient height or patient weight did not differ with the use of prone positioning. Both groups had similar rates of chronic obstructive lung disease (COPD) and congestive heart failure (CHF).

In multivariable analysis adjusted for BMI and baseline total APACHE score, the presence of pneumonia was independently associated with prone positioning therapy (OR 1.90, 95% CI 1.11-3.23, p=0.022) ***(*Table 2).*** Persistent hypoxemia after 24 hours of ARDS onset was associated with increased prone positioning (OR 2.32, 95% CI 1.45-3.71, p=0.002). Severe ARDS on initial diagnosis (Baseline PaO_2:F_IO_2 <100 mmHg) was also positively associated with proning (OR 1.77, 95% CI 1.17-2.6, p= 0.0181). Markers of hemodynamic instability – hypotension (baseline MAP <65) and cardiovascular SOFA score – were not associated with proning.

Discussion

This study is the first study to investigate the patient-level factors associated with prone positioning among U.S. patients with moderate-to-severe ARDS. The primary findings are that the presence of pneumonia, persistent hypoxemia and severe ARDS were independently

associated with prone positioning use. Proned patients were twice as likely to have persistent hypoxemia and were more likely to have severe ARDS, need for RRT and use of vasoactive agents compared to patients who were not proned. Markers of hemodynamic instability – hypotension (baseline MAP <65) and cardiovascular SOFA score – were not associated with proning.

Guerin et al performed an international prevalence study (APRONET) predominantly in European ICUs aimed at understanding the use of proning in ARDS and factors related to not proning among patients who were eligible.[23] The prevalence of proning was 40.2% in those who met PROSEVA criteria and 32.9% in patients who had severe ARDS. Moderate-to-severe ARDS defined as PaO2/ FiO2 < 150 (vs. PaO2/ FiO2 >150) (OR 0.34, 95% CI 0.19-0.61), tidal volume (Vt)< 6 ml/kg predicted body weight (PBW) (vs. Vt > 6 ml.kg) (OR 0.56, 95% CI 0.35-0.89) and PEEP > 10 (vs. PEEP <10) (OR 0.38, 95% CI 0.23-0.64) at the time of inclusion were significantly with a lower probability of proning not being used (ie. greater likelihood of proning). Higher Simplified Acute Physiologic Score (SAPS) II (OR 1.04, 95% CI 1.03-1.05) and higher Pplat values (OR 1.07, 95% CI 1.04-1.11) were associated with a higher probability of proning not being used (ie. greater likelihood of not proning). The two most common reasons listed by clinicians for not proning included the perception that hypoxemia was not severe enough to justify proning and concern regarding hemodynamic stability (too unstable to prone). This suggests that clinicians have potential misconceptions regarding the safety of proning or that clinicians continue to reserve prone positioning as rescue therapy in severe ARDS. The findings in this study, along with the current study, that worsening hypoxemia and severe ARDS are associated with proning would be consistent with the thought that clinicians are using proning as salvage therapy and not per guideline recommendations. The prevalence of proning

was 13% in this cohort which is similar to LUNGSAFE (16%) in severe ARDS although both are substantially lower than the prevalence of 32% found in APRONET. This difference in the use of proning in ROSE (13%) and LUNGSAFE compared to APRONET could reflect practice differences as most of the ICUs in APRONET were located in European countries who are strong proponents of proning and have conducted most of the large clinical trials thus far on proning.

Pneumonia could represent a sub-phenotype of ARDS with lower PaO_2:F_IO_2 ratios that reflects patients who clinicians' perceive to benefit from prone positioning therapy. Additionally, rapidly improving ARDS (RiARDS)- ARDS that resolves within 1 day- is an increasingly prevalent and distinct phenotype and it has been shown that 1 in 14 patients with severe ARDS at screening had resolved ARDS on study day 1.[24] The strong association of persistent hypoxemia and proning in our study raises the question of whether this reflects the limitation of identifying RiARDS at study enrollment and further highlight the rationale of PROSEVA to enroll patients only if they continued to meet inclusion criteria after 12-24h of stabilization.[19] Although obesity was identified by clinicians as a reason for not proning in a small number of patients in APRONET, we did not see a significant difference by BMI or weight in this study and APRONET did not find a statistically significant association with BMI in bivariate analysis. This could be due to fear of complications in obese patients with process of proning, however it has been shown that obese patients can be safely proned.[25] Additionally although clinicians voiced concern about hemodynamic instability as a reason to not prone in APRONET, we did not find associations between markers of hemodynamics (hypotension and cardiovascular SOFA score) and proning.

Our study had several strengths. We had robust and complete data on the outcome and most factors of interest. Additionally, a wide range of academic and community centers were represented from around the U.S. which strengthens generalizability. Lastly, given the entire cohort was diagnosed with ARDS, the concern of under recognition of ARDS leading to underutilization of therapies which had been identified as a leading concern in LUNGSAFE was not a factor in this study.

Limitations include the lack of data on system-level factors such as staffing models and ARDS case volume and provider-level factors such as recognition of ARDS and provider beliefs and predilections for use of prone positioning. However, evaluating patient-level factors in a robust cohort is vastly informative and future studies can focus on qualitative and qualitative approaches to gathering provider and system-level factors for investigation. We had substantial missing data on important data points such as use of renal replacement therapy and plateau pressure measurements which precluded study of these factors in our analysis.

This study demonstrated that patient level factors associated with proning correspond to the reasons to not prone identified in prior studies. These include persistent or severe hypoxemia and pneumonia as an etiology of ARDS. The results further highlight that there are likely significant provider and system level factors driving how critical care providers utilize proning in ARDS. A lack of knowledge of the criteria recommended for proning, risk of complications and the evidence for proning could be a significant provider-level barrier to proning. Site-level factors such as the presence of an ARDS treatment algorithm, education programs around the process of proning for clinical providers and best practice measures for ARDS could affect the use of proning. Further investigations on these factors and qualitative studies aimed at understanding provider experiences and beliefs regarding proning are especially important as the

coronavirus 2019 (COVID-19) pandemic has brought increasing attention to the use of proning in ARDS.[26] Future studies should focus on identifying barriers and facilitators to proning at a provider and system level as this will be key to increase proning in severe ARDS.

In conclusion, prone positioning is more likely to be utilized in severe and persistent ARDS suggesting the consistent use of proning as a salvage therapy opposed to guideline recommendations.

Table 1. Patient and clinical characteristics by receipt of prone positioning			
Characteristic	Not proned (n=846)	Proned (n=128)	p-value
Age- yr	56 (15)	54 (15)	0.10
Male sex	472(56%)	71 (55%)	0.95
White race	586 (69%)	92 (72%)	0.55
BMI- kg/m^2	33.3 (13.5)	32.4(10.4)	0.49
Weight, kg	95.3 (39.2)	94.1 (30.9)	0.74
Co-morbidities			
COPD[a]	160 (19%)	23 (18)	0.88
Missing	29	7	
Congestive heart failure	74 (9%)	7 (6%)	0.24
Missing	29	8	
Primacy cause of lung injury			
Pneumonia	625 (74%)	110 (86%)	**0.003**
Aspiration	215 (26%)	33 (26%)	0.93
Non-pulmonary sepsis	465 (55%)	76 (59%)	0.35
Other causes[b]	162 (19%)	25 (19%)	0.92
Use of vasopressors on day 1	557 (66%)	92 (72%)	0.32
Missing	34	2	
Use of vasopressors on day 2	436 (52%)	77 (64%)	0.11
Missing	73	8	
Initiation of RRT[c]	194 (23%)	36 (28%)	0.80
Missing	581	80	
Persistent hypoxemia[d]	115 (14%)	37 (28%)	**<0.001**
Assessments and measurements			
Baseline Total SOFA score[e]	8 (6-11)	8 (6-11)	0.69
Baseline APACHE III score [f]	104 (30.1)	109.4 (30.9)	0.07
Baseline PaO_2:F_IO_2 – mm hg [g]	300 (38%)	62 (50%)	**0.015**
Baseline MAP <= 65 [h]	638 (75%)	91 (73%)	0.30
Missing	18	3	
Baseline plateau pressure – cm of water	25.5 (5.8)	25.5 (7.0)	0.93
Missing	408	48	
Baseline cardiovascular SOFA score	3 (1-4)	3 (1-4)	0.74
Missing	21	1	
Died, N (%)	353 (42%)	58 (45%)	0.73

[a] Chronic Obstructive Lung Disease (COPD)

[b] Trauma, multiple transfusions, influenza, heroin overdose, pancreatitis, usual interstitial pneumonia (UIP), inhalation injury, non-cardiogenic shock, cardiac arrest

[ch] Renal replacement therapy (RRT)

[d] Persistent hypoxemia is defined as PaO_2:$F_IO_2 \leq 150$ and $FiO2 \geq 0.6$

[e] Sequential Organ Failure Assessment (SOFA) scores

[f] Acute physiologic assessment and chronic health evaluation (APACHE III) scores

[g] Ratio of partial pressure of arterial oxygen to fractional inspired oxygen (PaO_2:F_IO_2); coded as a binary variable- severe ARDS (P/F < 100)

Mean arterial pressure (MAP)

Numeric variables summarized by mean (SD) or median (Q1-Q3)

Categorical variables summarized by N (%)

If missing data is present, it is listed below the numeric summary statistics or included as a level for categorical variables

Table 2. Association between patient demographic and clinical characteristics and receipt of prone positioning therapy within 48 hours of ARDS onset, as estimated using multivariable logistic regression		
Variable	OR (95% CI)[a]	p-value
Pneumonia[b]	1.90 (1.11- 3.23)	0.022
Persistent hypoxemia[c]	2.32 (1.45-3.71)	0.002
Baseline PaO_2:F_IO_2[d]	1.77 (1.17-2.66)	0.018
Baseline MAP < 65 mmHg	0.67 (0.42-1.07)	0.11
Baseline cardiovascular SOFA score	0.91 (0.79-1.04)	0.16
[a] adjusted for BMI and baseline total APACHE score [b] Binary variable (Pneumonia as primary or secondary cause of lung injury) [c] Persistent hypoxemia is defined as PaO_2:$F_IO_2 \leq 150$ and $FiO2 \geq 0$. [d] Binary variable (Severe ARDS- PaO_2:F_IO_2 <100 mmHg		

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