Original Article

Physiological effect of prone positioning in mechanically ventilated SARS-CoV-2- infected patients with severe ARDS: An observational study

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Abstract

Background and Aims: Mechanical ventilation in prone position was associated with a reduction in mortality and increase in arterial oxygenation in acute respiratory distress syndrome (ARDS) patients. However, physiological effects of prone position in COVID ARDS patients are unknown.

Material and Methods: In this prospective observational study, data of n = 47 consecutive real time RT- PCR confirmed SARS-CoV-2-infected patients with severe ARDS were included. Respiratory mechanics and oxygenation data of recruited patients were collected before and after prone position.

Results: Median (Interquartile range, IQR) age of the recruited patients was 60 (50–67) years and median (IQR) PaO_2/FiO_2 ratio of 61.2 (54–80) mm Hg with application of median (IQR) positive end expiratory pressure (PEEP) of 12 (10–14) cm H2O before initiation of prone position. Out of those patients, 36 (77%) were prone responders at 16 hours after prone session, evident by increase of PaO2 by at least 20 mm Hg or by 20% as compared to baseline, and 73% patients were sustained responders (after returning to supine position). Plateau airway pressure ($p < 0.0001$), peak airway pressure ($p < 0.0001$), and driving pressure ($p < 0.0001$) were significantly reduced in prone position, and static compliance ($p = 0.001$), PaO_2/FiO_2 ratio ($p < 0.0001$), PaO_2 ($p = 0.0002$), and SpO_2 ($p = 0.0004$) were increased at 4 hours and 16 hours since prone position and also after returning to supine position.

Conclusion: In SARS-CoV-2-infected patients, mechanical ventilation in prone position is associated with improvement in lung compliance and oxygenation in almost three-fourth of the patients and persisted in supine position in more than 70% of the patients.

Keywords: ARDS, COVID-19, prone position, respiratory mechanics, SARS-CoV-2

Introduction

Since the diagnosis of the first case in December 2019, more than 20 million people across the globe has been infected by SARS-CoV-2 virus. Data of more than 70,000 suspected or confirmed such patients reported that nearly 20% of all laboratory confirmed cases had severe disease or critical illness.[1] Reported case fatality rate (CFR) from SARS-CoV-2 is widely variable; population data from Coronavirus Resource Center of Johns Hopkins University

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reported CFR between 0.8% and 8%. However, mortality in critically ill patients is higher and a recent meta-analysis reported that all-cause intensive care unit mortality is around 35%.[2] The researchers from Italy proposed two different phenotypes of ARDS in COVID-19 pneumonia patients; the 'L' phenotype has normal lung weight and compliance and hypoxemia occurs due to the loss of hypoxic pulmonary vasoconstriction. The 'L' phenotype may later progress to 'H' phenotype with increased lung weight and low compliance.[3]

Guérin *et al*.[4] reported that mechanical ventilation in prone position was associated with reduced mortality and improvement in oxygenation in severe acute respiratory distress syndrome (ARDS) patients with PaO_2/FiO_2 (P/F) ratio < 150 mm Hg. In such patients, prone ventilation for at least 16 hours per session decreased 28-day mortality by nearly 50% without any increase in complications. Prone position improves lung aeration more homogenously by recruiting dorsal alveoli, reduces lung strain and stress, and leads to improvement in oxygenation.[5] Pathophysiology of SARS-CoV-2-associated ARDS is different from ARDS that resulted from other causes with predominantly peripheral involvement in COVID-ARDS. Hence, this study was planned to know the physiological effect of prone position in SARS-CoV-2-associated ARDS patients.

Material and Methods

After obtaining Permission from the Institute Ethics Committee obtained on July 15, 2020 (No. IEC-677/03.07.2020, RP- 43/2020) and informed consent from legally acceptable representative of all recruited patients, data of n = 47 consecutive real time RT-PCR confirmed SARS-CoV-2 patients with severe ARDS were recruited. Patients were recruited immediately when they fulfilled the criteria of 'prone position.' A preliminary analysis of this research, that contained data of 20 patients, was made available under a CC-BY-NC-ND 4.0 International license preprint in medRxiv preprint server (DOI: https://doi.org/10.1101/2020.09.16.20195958, this version was posted on September 18, 2020).

Primary objective of this observational study was to know changes in respiratory mechanics and oxygenation parameters with prone position. Secondary objectives were to identify risk factors of no response from prone mechanical ventilation.

As per our intensive care unit protocol, all ARDS patients on mechanical ventilation with $PaO_2/FiO_2 < 150$ were placed in at least 16 h/day prone session for consecutive days till the criteria is met, unless there are contraindications of prone position. Both intravenous sedation and neuromuscular blocking agents were continued throughout the prone position. We followed the 'prone position' technique described by Guérin *et al*.[4] and no thoraco-pelvic support was used. Demographic characteristics, blood gas and respiratory mechanics data were collected at baseline before initiation of prone session, at 4 hours and 16 hours of prone position and after 4 hours of returning to supine position. Positive end expiratory pressure (PEEP) was titrated as per PEEP-FiO_2 table of *ARDSNet protocol*; however, PEEP was not increased if it was associated with worsening static compliance. Prone responders were defined by 20% increase in PaO_2/FiO_2 ratio during the prone session and sustained responders were defined by 20% increase in PaO_2/FiO_2 ratio compared to baseline at 4 hours after returning to supine position.

Non-parametric data were presented as median and IQR (inter-quartile range) and categorical data were presented as absolute numbers or percentages. Unpaired data between prone responders and non-responders were compared by Chi-square test or Mann–Whitney U test as applicable. All analyses were performed by a single study author (SM).

Predictors of prone response were identified by plotting receiver operating characteristic curve and area under the ROC curve with best cut-off value (as per Youden's index) were reported. Longitudinal data were compared by Friedman's test and multiple comparisons were performed by Wilcoxon matched pair sign rank test. A two-sided P value <0.05 was considered as significant. All statistical analyses were performed using Stata version 13 for Mac OS, (*StataCorp. 2011. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP*.).

Results

In this study, data of n = 47 patients were analyzed with a median (IQR) age of 60 (50-67) years, median (IQR) predicted body weight of 58 (55-62) kg and a median (IQR) Sequential Organ Failure Score (SOFA) of 7 (5-9). All included patients suffered from severe ARDS with median (IQR) P/F ratio of 61.2 (54-80) mm Hg with a median (IQR) PEEP of 12 (10-14) before initiation of prone ventilation. About 77% (95% CI 63-86%) patients were prone responders at 16 hours prone session and 73% (95% CI 58-83%) patients were sustained prone responders after returning to supine position. Prone responders had significantly higher respiratory static compliance at baseline (18 vs. 10 ml/cm H2O, P = 0.02, Mann–Whitney U test) but all other blood gas and respiratory mechanics variables were similar between responders and non-responders at baseline [Table 1]. Median [IQR] number of prone ventilation

Table 1: Respiratory Mechanics data at the time of enrolment (before prone position)

Parameters	All patients *n*=47	Responders *n*=36	Non-responders *n*=11	Significance (*P*)
Demographic characteristics and SOFA score				
Age (years) Median (IQR)	60 (50-67)	57.5 (47.5-65)	65 (52-70)	0.11
Predicted Body weight (Kg) Median (IQR)	58 (55-62)	58.5 (56-62)	58 (64-60)	0.35
Sex (Male/Female)	38/9	29/7	9/2	0.93
SOFA Median (IQR)	7 (5-9)	7 (5-9)	8 (5-9)	0.48
Respiratory mechanics				
Tidal Volume (ml) Median (IQR)	360 (350-380	360 (350-380)	360 (340-400)	0.81
Peak airway pressure (cm H_2O) Median (IQR)	44 (38-50)	44 (40.5-48.5)	48 (36-52)	0.51
Plateau pressure (cm H_2O) Median (IQR)	32 (28-36)	32 (28-36)	34 (28-36)	0.63
Static compliance (ml/cm H_2O) Median (IQR)	16 (12-21)	18 (13-22)	10 (8-12)	0.02*
PEEP (cm H_2O) Median (IQR)	12 (10-14)	12 (10-14)	10 (8-12)	0.01*
Driving Pressure (cm H_2O) Median (IQR)	20 (17-24)	20 (17-24)	24 (17-26)	0.18
Respiratory Rate (per minute) Median (IQR)	25 (24-28)	25 (24-28)	28 (24-30)	0.35
Arterial Blood gases				
pH median (IQR)	7.31 (7.24-7.38)	7.315 (7.244-7.38)	7.3 (7.21-7.4)	0.94
$PaCO_2$ (mm Hg) Median (IQR)	47.4 (38-58)	47.4 (38.45-58)	46 (33.4-65)	0.63
PaO_2 (mm Hg) Median (IQR)	57.5 (52-71)	57.25 (51.5-69.5)	66 (25-90)	0.94
SpO_2 (%) Median (IQR)	89 (86-91)	89 (86-91)	89 (84-94)	>0.99
PaO_2/FiO_2 ratio (P/F ratio in mm Hg) Median (IQR)	61.2 (54-80)	59.3 (53.75-73.5)	79 (54-110)	0.13
Vasopressor requirement				
Noradrenaline infusion (mcg/Kg/minute) Median (IQR)	0 (0-5)	0 (0-5)	0 (0-5)	>0.99

session used was four[3-5] per patient. Median [IQR] ICU length of stay was 10 [7-14] days. Survival rate (95% CI) was 30.1 (18-46.9) % among prone responders whereas none of prone non-responders survived.

As compared to baseline, there was a significant decrease in plateau airway pressure ($p < 0.001$), peak airway pressure ($p < 0.001$), and driving pressure ($p < 0.001$) and increase in static compliance ($p < 0.001$) at 4 hours and 16 hours after initiation of prone session and also after the return to supine position [Figure 1]. In addition to the change in respiratory mechanics, PaO_2/FiO_2 ratio ($p < 0.0001$), PaO_2 ($p = 0.0002$), and SpO_2 ($p = 0.0004$) were increased from baseline and persisted 4 hours after return to supine position [Figure 1]. However, arterial $PaCO_2$ levels and pH did not change significantly during prone ventilation. Noradrenaline requirement did not change significantly during the prone session ($p = 0.20$). Percentages of changes in static compliance significantly correlated with PaO_2/FiO_2 ratio at 16 hours prone ($r^2 = 0.36$, $P = 0.01$) and after returning to supine position ($r^2 = 0.41$, $P = 0.004$), but not at 4 hours ($p = 0.68$).

Baseline plateau pressure of ≥26 cm H_2O poorly predicted the probability of being non responders with 100% sensitivity with AUC (Area Under the Curve) of ROC (Receiver Operating Curve) area of 0.55 (SE = 0.09, 95% CI 0.35-0.74). Baseline static compliance was a predictor of prone response with reasonable accuracy [AUROC (95% CI) 0.726 (0.53-0.92)], with static compliance ≥11 ml/cm H_2O predicting responders with 89% sensitivity and 55% specificity. Baseline driving pressure (DP) ≥21 cm H_2O predicted probability of being non-responder with almost 72% sensitivity and 58% specificity (AUROC 0.63, CI 0.42-0.83). A value of plateau pressure ≤30 cm H_2O had sensitivity of 70.59% and specificity of 46% in predicting sustained responders. Sustained responders had persisted compliance ≥11 cm H_2O [sensitivity 85%, specificity 38% (AUROC 0.59, CI 0.40-0.78)] [Figure 2]. Prognostic performance of various respiratory mechanics parameters to predict prone response was depicted in Table 2. Overall survival (95% CI) in the cohort was 23.4 (13.6-37.2) %.

Discussion

We observed that more than three-fourth of the SARS-CoV-2-infected patients with severe ARDS had improved oxygenation with 16 hours prone position ventilation. An improvement in lung mechanics such as plateau pressure, driving pressure, and static compliance was also observed without any change in the hemodynamic support, $PaCO_2$ level, and acid base status.

A study conducted in the United States, where mechanical ventilation in prone position was used in 62 patients with COVID-ARDS, reported improvement in physiological

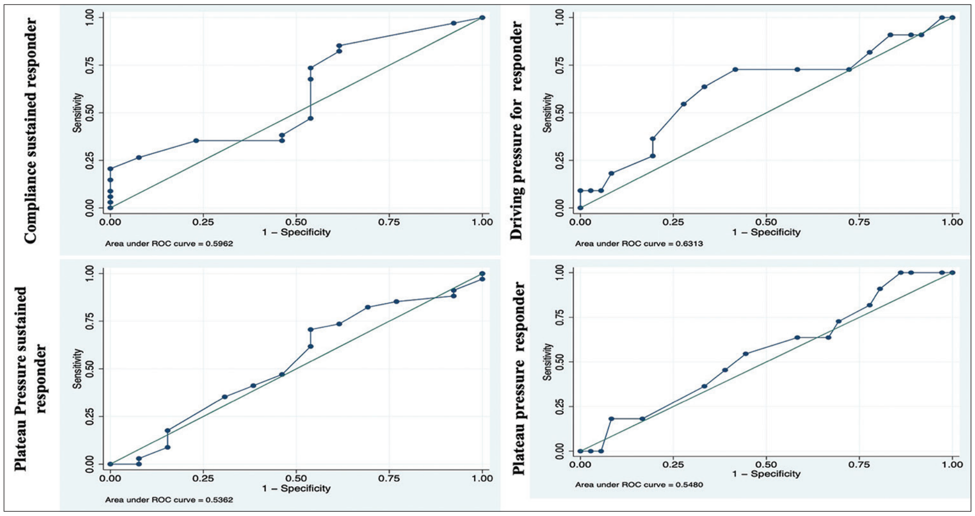

Figure 1: Plateau pressure, Driving pressure, PaCO2, and P/F ratio at baseline, 4 hours and 16 hours of prone positioning and 4 hours after supine position

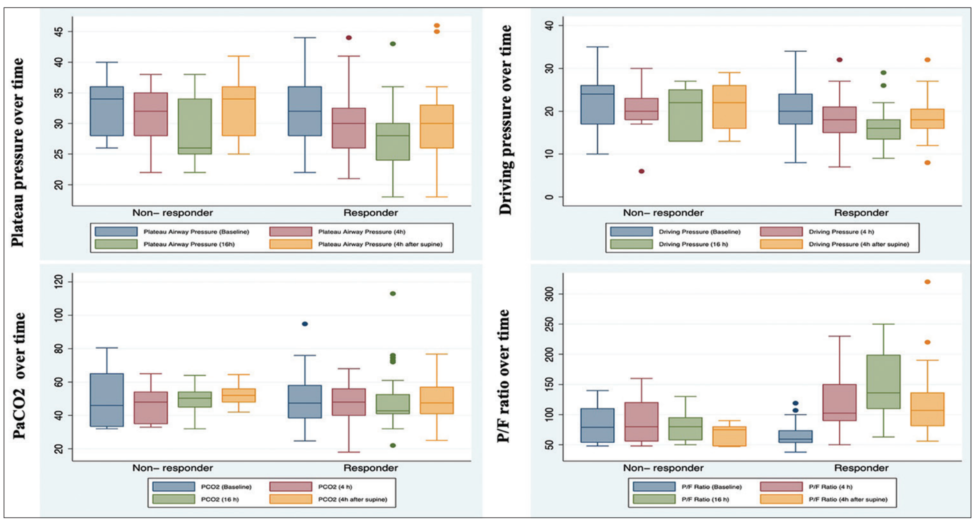

Figure 2: Area under the receiver operating characteristics (AUROC) curves of different parameters to predict response to prone positioning

parameters with prone position.[6] Another small physiological study also reported improvement in PaO_2/FiO_2 ratio and decrease in PEEP requirement in prone position[7] in these patients. In the current series, all the patients in this study had reduced static respiratory compliance and this is in contrary to the findings reported from Italy. Though the changes in respiratory compliance in prone position in ARDS patients are not uniform,[8] we have found a significant decrease in driving pressure and improvement in static compliance in prone position. Recruitment of the dorsal lung regions was the biological plausibility behind the improvement in static compliance as both compliance and driving pressure were correlated with change in PaO_2/FiO_2 ratio.[9] Moreover, these correlations were maintained even after the return to supine position indicating sustained lung recruitment in SARS-CoV-2-infected patients. It is important to determine the baseline static compliance as it was a decent predictor of prone non-response and therefore, these patients may be considered to extra-corporeal membrane oxygenation early in the course of disease.

Reported mortality in mechanically ventilated COVID-ARDS patients is around 75%[10] which is similar to our findings. Mortality from COVID-ARDS is higher than non-COVID-ARDS patients. Bellani *et al.*[11] in 2016 reported 28-day mortality around 41% in severe ARDS patients.

Most important limitation was the small sample size. Moreover, we did not use esophageal manometer and therefore could not assess the effect of prone position on chest wall and lung compliance separately.

Table 2: Predictive ability of various respiratory mechanics parameters

Response to prone position	Parameter	Cut-off	Sensitivity	Specificity	AUROC (95% CI)
Responder	Plateau pressure	≤26 cm H_2O	100%	13.89%	0.548 (0.35-0.74)
	Driving pressure	≤21 cm H_2O	72.73%	58.53%	0.63 (0.42-0.83)
	Static compliance	≥11 ml/H_2O	88.89%	54.55%	0.72 (0.53-0.91)
Sustained Responder	Plateau pressure	≤30 cm H_2O	70.59%	46.15%	0.53 (0.33-0.75)
	Static compliance	≥11 ml/cm H_2O	85.29%	38.4%	0.59 (0.40-0.79)
	Driving pressure	≤18 cm H_2O	76.47%	38.46%	0.45 (0.23-0.67)

Conclusion

In mechanically ventilated SARS-CoV-2-infected severe ARDS patients, prone position is associated with improvement in lung compliance and oxygenation in almost three-fourth of the patients and persistence after returning to supine position in more than 70% of patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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