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Effect of the prone position on recruitability in acute respiratory distress syndrome due to COVID-19 pneumonia

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SUMMARY

OBJECTIVE: This study aimed to assess the effect of prone position on oxygenation and lung recruitability in patients with acute respiratory distress syndrome due to COVID-19 receiving invasive mechanical ventilation.

METHODS: This prospective study was conducted in the intensive care unit between December 10, 2021, and February 10, 2022. We included 25 patients admitted to our intensive care unit with acute respiratory distress syndrome due to COVID-19 who had undergone prone position. We measured the respiratory system compliance, recruitment to inflation ratio, and PaO_2/FiO_2 ratio during the baseline supine, prone, and resupine positions. The recruitment to inflation ratio was used to assess the potential for lung recruitability.

RESULTS: In the prone position, PaO_2/FiO_2 increased from 82.7 to 164.4 mmHg ($p<0.001$) with an increase in respiratory system compliance ($p=0.003$). PaO_2/FiO_2 decreased to 117 mmHg ($p=0.015$) in the resupine with no change in respiratory system compliance ($p=0.097$). The recruitment to inflation ratio did not change in the prone and resupine positions ($p=0.198$ and $p=0.621$, respectively). In all patients, the median value of respiratory system compliance during supine was 26 mL/cmH_2O. In patients with respiratory system compliance<26 mL/cmH_2O (n=12), respiratory system compliance increased and recruitment to inflation decreased from supine to prone positions ($p=0.008$ and $p=0.040$, respectively), whereas they did not change in those with respiratory system compliance ≥26 mL/cmH_2O_8 (n=13) ($p=0.279$ and $p=0.550$, respectively) (ClinicalTrials registration number: NCT05150847).

CONCLUSION: In the prone position, in addition to the oxygenation benefit in all patients, we detected lung recruitment based on the change in the recruitment to inflation ratio with an increase in respiratory system compliance only in acute respiratory distress syndrome due to COVID-19 patients who have <26 mL/cmH_2O baseline supine respiratory compliance.

KEYWORDS: COVID-19. Acute respiratory distress syndrome. Mechanical Ventilation. Prone position.

INTRODUCTION

Prone positioning improves oxygenation by distributing ventilation more homogeneously, improving ventilation-perfusion matching, decreasing venous admixture, reducing lung compression, and limiting ventilator-induced lung injury in patients with acute respiratory distress syndrome (ARDS)[1-7]. Early data on COVID-ARDS showed severe hypoxemia with near-normal respiratory compliance[8]. However, the physiological effects of the prone position on static compliance and oxygenation were not differentiated between the patients with and without COVID-ARDS[9,10].

The prone position may affect respiratory mechanics by varying lung recruitability and compliance[5,10-13]. Static compliance of the respiratory system increases during the prone position when accompanied by high positive end-expiratory pressure (PEEP) levels but not with low PEEP in non-COVID-ARDS[5]. In a study with COVID-19 patients, the prone position did not improve static compliance[10]. In a study by Cour et al., including COVID-19 patients with ARDS, high recruiters had better compliance of the respiratory system in addition to oxygenation in the prone position, while low recruiters had better oxygenation only[12]. The measurement of recruitability was proposed to predict alveolar recruitment induced by PEEP[14]. A novel bedside technique, known as the recruitment to inflation (R/I) ratio, can estimate the high or poor potential for lung recruitment in patients receiving invasive mechanical ventilation (IMV)[14]. In a study by Pan et al., including COVID-19 patients, the R/I ratio increased with prone ventilation[15]. In another study with COVID-19 patients, the R/I ratio decreased in high recruiters during prone ventilation with increased Cs and oxygenation[12]. The decrease in R/I ratio with increased Cs and oxygenation was explained by accurate lung recruitment with prone ventilation[12]. We conducted this study to assess the effect of the prone position on oxygenation, Cs, and the R/I ratio in patients with COVID-ARDS receiving IMV.

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METHODS

Patients with COVID-19 older than 18 years of age who were intubated, sedated, and receiving IMV due to moderate-to-severe ARDS between December 10, 2021, and February 10, 2022, were screened if they met the ARDS criteria according to the published consensus conference on the definition of ARDS[16]. The patients who had partial oxygen/inspired oxygen fraction (PaO_2/FiO_2) less than 150 mmHg and had undergone prone positioning were included. Prone positioning was accepted to be indicated if ARDS patients receiving IMV had PaO_2/FiO_2 of less than 150 mmHg. Exclusion criteria were the presence of obstructive lung disease history, chest wall abnormalities, interstitial lung disease, pneumothorax, pregnancy, hemodynamic instability refractory to a vasoactive drug (mean arterial blood pressure <65 mmHg lasting more than 1 h, not responsive to noradrenaline>0.5 µg/kg/min), and a history of pneumonectomy or lobectomy. This prospective study was conducted in a tertiary hospital's intensive care unit (ICU). The Tepecik Training and Research Hospital Local Ethics Committee approved the study protocol (No: 2021/11-02), and written informed consent was obtained from the patients and/or the nearest kin of the patients (ClinicalTrials registration number: NCT05150847).

All patients received volume-controlled mechanical ventilation with a tidal volume (VT) of 6–8 mL/kg of predicted body weight, keeping the inspiratory plateau pressure (Pplat) below 30 cmH_2O, respiratory frequency of 12–20 breaths/min, inspiratory time to expiratory time ratio (I/E) 1:2, and FiO_2 level that kept arterial PaO_2 between 60 and 80 mmHg. If the pH was less than 7.25 with low VT and adequate breathing frequency, the Pplat limit was allowed to reach up to 35 cmH_2O. In all patients, clinically set PEEP was the minimum PEEP associated with PaO_2 ranging from 60 to 80 mmHg, aiming a FiO_2 of ≤0.60 while avoiding adverse effects such as hypotension, severe acidosis, and Pplat>30 cmH_2O. All patients were deeply sedated. Patients received neuromuscular blocking agents when needed.

Patients were included in the study within 48 h of intubation. Prone positioning was performed over 16 h in patients whose PaO_2/FiO_2 was less than 150 mmHg. The oxygenation and respiratory mechanics were monitored in the supine, prone, and resupine positions. Respiratory mechanics and arterial blood gas (ABG) measurements were repeated at 6–8 h in the supine position, 12–16 h in the prone position, and 6–8 h in the resupine position. The R/I ratio, ABG measurements, Pplat, static compliance [Cs; VT/(Pplat-PEEP)], and driving pressure (Pplat-PEEP) were recorded in each season. Pplat was obtained using an inspiratory pause maneuver. Airway opening pressure (AOP) was determined during a low-flow insufflation (4 L/min) period of the pressure-volume curve, as described previously[14]. The R/I ratio measurement was performed based on a study by Chen et al.[14]. According to this technique, PEEP was changed from the baseline level to 15 cmH_2O. Then, the change in end-expiratory lung (ΔEELV) volume was measured by a single-breath PEEP reduction from 15 to 5 cmH_2O[14] with a respiratory rate of 10/min to eliminate possible auto-PEEP. If the AOP detected by a low-flow pressure-volume curve was higher than>5 cmH_2O PEEP, this measured AOP was used for measurement. During the single-breath PEEP reduction maneuver, ΔEELV was calculated by subtracting the expired tidal volume from the first expired volume detected when PEEP decreased abruptly from 15 to 5 cmH_2O[14]. The recruited lung volume (Vrec) was calculated as ΔEELV—minimal predicted ΔEELV. The minimally predicted ΔEELV was calculated as Cs at 5 cmH_2O PEEP (or AOP)×ΔPEEP (i.e., 15 cmH_2O - 5 cmH_2O (or AOP)). The recruited lung compliance (CRec) was calculated as Vrec/ΔPEEP. The R/I ratio was calculated as Crec/Cs at low PEEP (5 cmH_2O or AOP). During the single breath maneuver for measuring and calculating the R/I ratio, Vrec, Cs, the same tidal volume, and respiratory rate settings were used. In post hoc analysis, we classified patients into two groups according to the median Cs at baseline supine position. The primary endpoint was the improvement in the PaO_2/FiO_2 ratio, and the secondary endpoints were the Cs and the R/I ratio.

The results are presented as the number (%), the mean±SD or median [interquartile range]. The data in the figures were drawn based on the median, interquartile range, and minimum-maximum range. A chi-square test was used for categorical variables. The t-test was used for continuous variables when data were normally distributed, and when the data were not normally distributed, the Mann-Whitney U test was used for comparing two groups. Paired measurements taken from the same individuals were compared using the paired samples t-test or Wilcoxon rank test, where appropriate. p-values ≤0.05 were considered statistically significant. Statistical analysis was performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

We screened 35 patients with laboratory-confirmed COVID-19 and moderate-to-severe ARDS for whom prone positioning was indicated during the study period. Three patients were hemodynamically unstable, two had septic shock requiring vasopressors, one had lung cancer, two had chronic obstructive lung disease, and two had pneumothorax. After excluding these 10 patients, 25 patients with moderate and severe

ARDS who had undergone prone positioning were included in the study. The median time between ICU admission and inclusion was 6 [2–7] days. Baseline patient characteristics are summarized in Table 1.

In the prone position, PaO_2/FiO_2 increased from a median of 73 [65–102] mmHg at baseline in the supine position to 156 [118–204] mmHg (p<0.001). In the resupine position, PaO_2/FiO_2 decreased to 117 [95–151] mmHg (p=0.015) (Table 2). In the prone position, the plateau pressure decreased from 24 [23–27] to 23 [21–24] cmH_2O (p<0.001). In the resupine position, the plateau pressure increased to 24 [22–26] cmH_2O (p=0.001). In the prone position, the driving pressure decreased from 13 [11–15] to 11 [9–13] cmH_2O (p<0.001). In the resupine position, the driving pressure increased to 13 [11–17] (p=0.002). In the prone position, the Cs increased from 26 [19–32] to 28 [22–38] mL/cmH_2O (p=0.003). In the resupine position, the Cs did not increase (p=0.097) (Table 2). There was no change in the Vrec (79 [49–154] for supine vs. 99 [67–122] for prone, p=0.393), Crec (8.2 [4.3–15.1] mL/cmH_2O for supine, 10.4 [6.7–12.9] mL/cmH_2O for prone, p=0.339), and R/I ratio in the prone position (0.39 [0.12–0.64] for supine vs. 0.36 [0.10–0.45] for prone, p=0.198). There was no change in the R/I ratio in the resupine position (0.36 [0.10–0.45] for prone, 0.24 [0.10–0.50] for resupine, p=0.621) (Table 2).

In post hoc analysis, patients were classified into two groups according to the median value of baseline supine Cs as Cs ≥26 mL/cmH_2O (n=13, median 31 [26–36] mL/cmH_2O) and <26 mL/cmH_2O (n=12, median 19 [16–20] mL/cmH_2O). We compared these two groups according to the median baseline Cs value, as there is no accepted threshold to consider Cs as high or low. There were no differences in age, sex, APACHE II score, body mass index, heart rate, or mean arterial pressure at inclusion between the two groups (Table 1). The median time between ICU admission and inclusion was 2 [1.5–6] days in the group with Cs ≥26 mL/cmH_2O and 7.5 [3–12] days in those with Cs<26 mL/cmH_2O (p=0.006). The days on noninvasive ventilation support before intubation were 2 [1–5] days in the group with Cs ≥26 mL/cmH_2O and 7 [2–11] days in those with Cs<26 mL/cmH_2O (p=0.009).

There was a higher R/I ratio in the baseline supine position in patients with Cs <26 mL/cmH_2O (p=0.050). The PEEP, $PaO_2/FİO_2$, Vrec, and Crec were not differentiated in Cs <26 mL/cmH_2O versus Cs ≥26 mL/cmH_2O at the baseline supine position (p=0.293, 0.814, 0.828, and 0.731, respectively). The PaO_2/FiO_2 was higher in Cs ≥26 mL/cmH_2O group than in Cs <26 mL/cmH_2O during the prone position (p=0.003). The PaO_2/FiO_2 increased from the supine to the prone position in both groups (p=0.001 for Cs ≥26 mL/cmH_2O and p=0.012 for Cs <26 mL/cmH_2O; Figure 1A, Table 2). The Cs increased from the supine to the prone position in both groups, but statistical significance was detected only in the Cs <26 mL/cmH_2O (p=0.008 vs. p=0.279). Vrec and Crec were not differentiated in Cs <26

Table 1. Baseline characteristics of all patients and comparison between the group with Cs ≥26 and <26 mL/ cmH_2O.

	All patients (n=25)	Cs ≥26 mL/cmH_2O group (n=13)	Cs <26 mL/cmH_2O group (n=12)	p-value*
Age, years	62.4±13.3	67.4±9.7	57.0±14.9	0.052
Female gender, n (%)	14 (56)	5 (38)	9 (75)	0.063
Body mass index, kg/m^2	32.0±5.7	32.2±5.7	31.9±6.3	0.977
APACHE II score	19.9±4.0	18.7±5.8	18.5±7.4	0.915
Heart rate, /min	86±20	83±19	93±21	0.196
Mean arterial pressure, mmHg	80 [70–88.5]	78 [69–86]	80 [71–91]	0.612
Preexisting disease				
Diabetes mellitus	10 (40)	6 (46)	4 (33)	0.688
Hypertension	11 (44)	5 (38)	6 (50)	0.561
Chronic renal failure	2 (8)	1	1	1.000
None	3 (12)	2	1	1.000
Between ICU admission to inclusion, days	6 [2–7]	2 [1.5–6]	7.5 [3–12]	0.006
Noninvasive support before intubation, days	5 [1–7]	2 [1–5]	7 [2–11]	0.009

Data are presented as the number (%), mean±standard derivation or median [interquartile range]. ICU: intensive care unit; APACHE: acute physiology and chronic health evaluation. *p-values refer to the comparison between the Cs ≥26 and Cs<26 groups.

Table 2. PaO_2/FiO_2, Cs, and R/I between Cs ≥26 and Cs <26 groups during supine, prone, and resupine positions.

	All patients	Cs ≥26	Cs<26	p-value*
PaO_2/FiO_2, mmHg				
Supine	73 [65–102]	75 [63–98]	72 [64–108]	0.814
Prone	156 [118–204]	200 [153–250]	124 [90–163]	0.003
Resupine	117 [95–151]	115 [99–153]	118 [81–128]	0.733
p-value**	<0.001	0.001	0.012	
p-value***	0.015	0.005	0.044	
Cs, mL/cmH_2O				
Supine	26 [19–32]	31 [26–36]	19 [16–20]	<0.001
Prone	28 [22–38]	35 [30–40]	22.5 [21–25]	<0.001
Resupine	29 [21–34]	33 [29–42]	21.3 [18–23.3]	<0.001
p-value**	0.003	0.279	0.008	
p-value***	0.097	0.613	0.090	
R/I ratio				
Supine	0.39 [0.12–0.64]	0.19 [0.12–0.49]	0.56 [0.10–0.75]	0.050
Prone	0.36 [0.10–0.45]	0.32 [0.10–0.44]	0.37 [0.11–0.47]	0.943
Resupine	0.24 [0.10–0.50]	0.37 [0.13–0.55]	0.29 [0.10–0.37]	0.164
p-value**	0.198	0.550	0.040	
p-value***	0.621	0.792	0.178	

Data are presented as the median [interquartile range]. PaO_2/FiO_2 mmHg: arterial oxygen partial pressure/fraction of inspired oxygen; Cs: static compliance; R/I ratio: recruitment to inflation ratio. *p-values detected by using Mann-Whitney U test refer to the comparison between the Cs ≥26 and Cs<26 groups. **p-values detected by using Wilcoxon rank test refer to the comparison of the parameter from supine to prone. ***p-values detected by using Wilcoxon rank test refer to the change between parameters from prone to resupine.

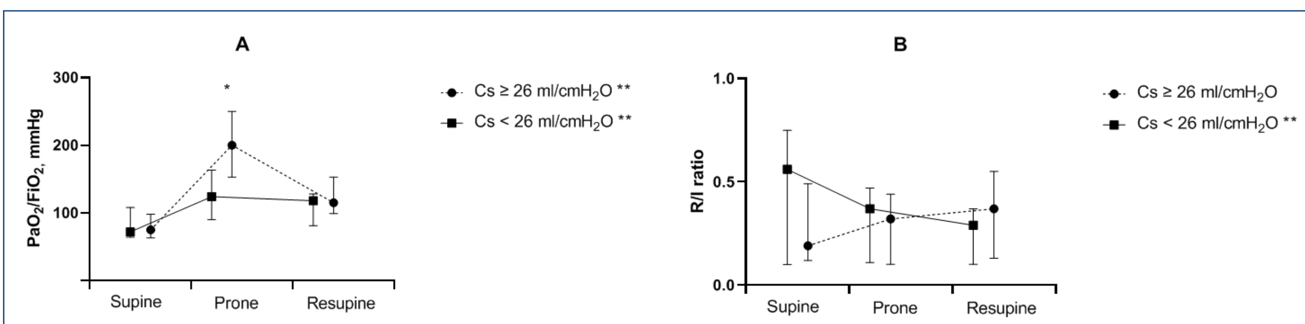

Figure 1. PaO_2/FiO_2 and R/I ratio between groups with Cs ≥26 mL/cmH_2O and Cs <26 mL/cmH_2O during supine, prone, and resupine positions. (A) *The PaO_2/FiO_2 was higher in Cs ≥26 mL/cmH_2O group than in Cs <26 mL/cmH_2O during the prone position (p=0.003). **The PaO_2/FiO_2 increased from the supine to prone position in both groups (p=0.001 for Cs ≥26 mL/cmH_2O and p=0.012 for Cs <26 mL/cmH_2O). (B) **The R/I decreased from the supine to prone position only in the Cs <26 mL/cmH_2O group (p=0.04), whereas it did not change in those with Cs ≥26 mL/cmH_2O (p=0.55). PaO_2/FiO_2 mmHg: arterial oxygen partial pressure/fraction of inspired oxygen; Cs: static compliance; R/I ratio: recruitment to inflation ratio.

mL/cmH_2O versus Cs ≥26 mL/cmH_2O at the baseline supine position (p=0.295, 0.819, 0.823, and 0.737, respectively). The R/I decreased from the supine to the prone position only in the Cs <26 mL/cmH_2O group (p=0.040), whereas it did not change in those with Cs ≥26 mL/cmH_2O (p=0.550, Figure 1B, Table 2).

DISCUSSION

This study found that the PaO_2/FiO_2 ratio increased both in the patients with higher and lower baseline supine compliance (Cs ≥26 and Cs<26 mL/cmH_2O). The recruitment to inflation ratio decreased in the prone position only in those with static compliance <26 mL/cmH_2O.

The group with Cs<26 mL/cmH_2O had a longer stay in the ICU on inclusion than those with Cs ≥26 mL/cmH_2O. All patients received noninvasive ventilation before intubation. The longer stays in the ICU with more prolonged use of noninvasive ventilation before intubation might explain the lower compliance due to impaired lung parenchyma. In COVID-19 patients, the oxygenation response to prone positioning and recruitment decreases over time, possibly due to the predominance of consolidation in the late stages compared with the early stages[17].

Measurement of the R/I ratio estimates the potential for lung recruitment at the bedside in mechanically ventilated ARDS patients[14-18]. The prone position may help recruit the injured lung even in patients with low potential for lung recruitment[5]. In this study, the low-compliance (median Cs <26 mL/cmH_2O) group exhibited a decreased R/I ratio with better oxygenation in the prone position than in the supine. Lung recruitment is consistent with a reduced R/I ratio and increased Cs during the prone position[12].

The decrease in the R/I ratio in Cs<26 mL/cmH_2O, but not in Cs ≥26 mL/cmH_2O, might reflect the differences in Cs and lung volume changes between the high- and low-compliance groups during the prone position. Although not statistically significant, there was a trend toward a reduction in the volume and compliance of the recruited lung in Cs<26 mL/cmH_2O during the prone position. According to these results, in Cs ≥26 mL/cmH_2O, the effect of prone positioning on the improvement of oxygenation could not be explained by lung recruitment, as there was no change in the R/I ratio and Cs. The oxygenation response may be primarily due to a more homogenous perfusion distribution in patients with Cs ≥26 mL/cmH_2O[13].

In their physiologic study, Pelosi et al. found no correlation between the change in Cs and the increase in PaO_2 during prone positioning in non-COVID-ARDS[19]. They also found significant improvements in Cs in the resupine position compared to the baseline supine. They concluded that improved oxygenation during prone positioning might be explained by regional lung volume changes, perfusion, and inflation/ventilation[19]. In a study with COVID-ARDS, improvement in oxygenation in the prone position was not associated with a change in Cs[10]. In this study, in addition to the significant improvement in Cs from the supine to the prone position, we found no change in Cs when returning to the supine from the prone position. The oxygenation slightly declined but was still higher than the baseline value, and the R/I ratio was maintained in the resupine position.

Our study had some limitations. It is a single-center study with a small sample size, and therefore confirmation of the results is required. The study was unblinded, and bias cannot be excluded. The severity of the disease and the influence of additional clinical conditions may be different in patients. The length of noninvasive support is a confounder that may influence the respiratory mechanics measured within 48 h postintubation.

In conclusion, in addition to the oxygenation benefit in all patients with prone position, we found that the R/I ratio was significantly reduced in the prone position with an increase in Cs, indicating recruitment benefit, only in patients with baseline compliance <26 cmH_2O in patients with COVID-ARDS requiring invasive mechanical ventilation.

ETHICAL STATUS

The Tepecik Training and Research Hospital Local Ethics Committee approved the study protocol (No: 2021/11-02), and written informed consent was obtained from the patients and/or nearest kin of the patients (ClinicalTrials registration number: NCT05150847). All authors declare that the study was conducted in accordance with the Declaration of Helsinki and followed the ethical standards of the country of origin.

AUTHORS' CONTRIBUTIONS

ÖE: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing. **KR:** Conceptualization, Formal Analysis, Methodology, Resources, Supervision, Visualization, Writing – review & editing. **HY:** Conceptualization, Data curation, Writing – review & editing. **RE:** Conceptualization, Data curation, Writing – review & editing. **IKG:** Conceptualization, Supervision, Writing – review & editing.

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