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Combined Effects of Prone Positioning and Airway Pressure Release Ventilation on Oxygenation in Patients with COVID-19 ARDS

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Abstract

Objective: Coronavirus disease 2019 (COVID-19) can cause acute respiratory distress syndrome (ARDS). Invasive mechanical ventilation (IMV) support and prone positioning are essential treatments for severe COVID-19 ARDS. We aimed to determine the combined effect of prone position and airway pressure release ventilation (APRV) modes on oxygen improvement in mechanically-ventilated patients with COVID-19.

Methods: This prospective observational study included 40 eligible patients (13 female, 27 male). Of 40 patients, 23 (57.5%) were ventilated with APRV and 17 (42.5%) were ventilated with controlled modes. A prone position was applied when the PaO_2/FiO_2 ratio <150 mmHg despite IMV in COVID-19 ARDS. The numbers of patients who completed the first, second, and third prone were 40, 25, and 15, respectively. Incident barotrauma events were diagnosed by both clinical findings and radiological images.

Results: After the second prone, the PaO_2/FiO_2 ratio of the APRV group was higher compared to the PaO_2/FiO_2 ratio of the control group [189 (150-237)] vs. 127 (100-146) mmHg, respectively, (P=0.025). Similarly, after the third prone, the PaO_2/FiO_2 ratio of the APRV group was higher compared to the PaO_2/FiO_2 ratio of the control group [194 (132-263)] vs. 83 (71-136) mmHg, respectively, (P=0.021). Barotrauma events were detected in 13.0% of the patients in the APRV group and 11.8% of the patients in the control group (P=1000). The 28-day mortality was not different in the APRV group than in the control group (73.9% vs. 70.6%, respectively, P=1000).

Conclusion: Using the APRV mode during prone positioning improves oxygenation, especially in the second and third prone positions, without increasing the risk of barotrauma. However, no benefit on mortality was detected.

Keywords: Airway pressure-release ventilation, ARDS, intensive care units, mortality, SARS-CoV-2

Main Points

- When combining prone positioning with airway pressure release ventilation (APRV), improvement in oxygenation is better than controlled mode, especially in the second and third prone positions.
- APRV can be safely used in Coronavirus disease-2019 (COVID-19) acute respiratory distress syndrome (ARDS) as barotrauma events are similar in both groups.
- APRV did not reduce mortality more than controlled modes in COVID-19 ARDS patients.

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Introduction

Coronavirus disease-2019 (COVID-19) is a pandemic caused by the severe acute respiratory syndrome. Coronavirus mainly affects the pulmonary system and can cause acute respiratory distress syndrome (ARDS).[1,2] The incidence of severe ARDS was 35% in mechanically ventilated intensive care unit (ICU) patients.[3] Mortality in COVID-19 patients with mild, moderate, and severe ARDS was 25, 33, and 41% respectively.[3] The survival advantage of prone position among patients with severe ARDS has been demonstrated in meta-analysis and randomized trials for a long-time.[4,5] In the supine position, since the dorsal trans-pulmonary pressure (airway opening pressure-pleural pressure) is higher than the ventral trans-pulmonary pressure, the ventral alveoli are prone to over-inflation and the dorsal alveoli are prone to atelectasis.[6] In the prone position, the difference between the dorsal and ventral trans-pulmonary pressure decreases and results in more homogeneous ventilation, lung aeration, and strain distribution than in the supine position.[7] Although ventilation distribution is affected by prone positioning, pulmonary perfusion is thought to be less affected by gravity.[8] Providing a better ventilation-perfusion match results in improved gas exchange, and a homogeneous distribution of ventilation results in a reduced risk of ventilator-induced lung injury.[7-9] Patients with COVID-19 ARDS have lung morphology and respiratory mechanics similar to patients with classical ARDS.[10] Mechanically ventilated COVID-19 patients with refractory hypoxemia were administered the prone position for rescue therapy,[3,11,12] resulting in improved oxygenation[3,11] and increased survival.[12]

Airway pressure-release ventilation (APRV) is an inverse ratio, pressure controlled, time-cycled, intermittent mandatory ventilation.[13] APRV delivers two levels of continuous positive airway pressure at which high pressure (P high) is delivered for a long duration (T high) and then falls to a lower pressure (P low) for a shorter duration (T low).[14] Maintaining a constant airway pressure (P high) for a long time (T high) ensures that multiple alveolar units are recruited, resulting in a greater surface area for gas exchange.[15] APRV permits spontaneous breaths at any time in the respiratory cycle.[13] Spontaneous breathing may improve the redistribution of ventilation to dependent lung areas, provide better ventilation/perfusion matching, improve venous return, and reduce the need for sedation and neuromuscular blockade.[16] APRV significantly increases the PaO_2/FiO_2 ratio and improves oxygenation in patients with ARDS compared with controlled methods.[17]

Overlapping physiological mechanisms that improve ventilation-perfusion mismatch in prone positioning and APRV may have potential synergistic effects on improving oxygenation in patients with COVID-19 ARDS. In this study, we evaluated the effects of combining APRV and prone positioning on gas exchange and mortality in patients with COVID-19 ARDS.

Methods

Study Population

After approval from the Local Ethics Committee of Dokuz Eylül University Non-Invasive Research Ethics Committee (date; 01.02.2021 and number; 2021/03-18) and the Turkish Ministry of Health, this prospective observational study was conducted in adult intensive care units of our center. All participants provided written informed consent. Between December 2020 and May 2021, all intubated patients (18 years and older) who met the Berlin criteria,[18] received both pronation and APRV or controlled mode interventions, and those diagnosed with COVID-19 were included in the study. SARS-CoV-2 infection was confirmed by either using a reverse transcriptase-polymerase chain reaction (RT-PCR) tested on respiratory samples or with clinical characteristics, laboratory, and computed tomography findings. Patients who did not meet the Berlin criteria and did not take the prone position after invasive mechanical ventilation (IMV) interventions were excluded from the study.

Definitions and Measurements

Our center uses APRV (Dräger Evita V300 and infinity V500, Lubeck, Germany) for patients with severe COVID-19-associated ARDS. APRV parameters were adjusted by an intensive care physician regarding previous guidelines.[15] It was aimed to maintain spontaneous breathing in the APRV group and was continuously monitored. Patients in the control group were ventilated according to the ARDSNet protocol. In our center, we applied the prone position when the PaO_2/FiO_2 ratio <150 mmHg despite IMV in COVID-19 ARDS. Prone positioning was performed in normal ICU beds. Patients with hemodynamic instability did not receive the prone position. Data on ICU-acquired infections included ventilator-associated pneumonia, bloodstream infections, and urinary tract infections. Incident barotrauma events, including new subcutaneous emphysema, pneumomediastinum, pneumopericardium, or pneumothorax were diagnosed by both clinical findings and radiological images. Sedation depth was assessed using the Richmond Agitation-Sedation Scale (RASS).[19] The sedation goal for most patients was a RASS score of -2 to +1.[19] For patients requiring deeper levels of sedation in the prone position, the most comfortable level that preserves spontaneous breaths was aimed for.

Variables

The demographic data (age, gender, smoking history, comorbidities), medical history, anthropometric measurements (Body Mass Index), Charlson Comorbidity Index (CCI), Acute Physiology and Chronic Health Evaluation (APACHE) II, and Sequential Organ Failure

Assessment (SOFA) scores were recorded. Blood pressure records were obtained from the first measurement of ICU admission. Disease characteristics for COVID-19 including RT-PCR results and blood tests were collected. The parameters of the mechanical ventilation and of the arterial blood gas analysis were recorded an hour before turning the patient to the prone position and within an hour following the prone episode. Sedative, analgesic, and muscle relaxant drugs were recorded in the prone periods. Complications such as emphysema, pneumothorax, hypotension, need for vasopressors, cardiac arrhythmia, vascular access removal, intubation tube removal, pressure ulcers, airway obstruction, corneal abrasion, oliguria, and anuria were recorded during prone position. Major events during ICU stay [presence of septic shock, ICU acquired infections, AKI, renal replacement therapy (RRT)] were recorded. Lengths of ICU and hospital stays, and mortality was recorded.

Outcomes

The primary outcome of the study was whether the combined use of APRV and prone positioning improves oxygenation in mechanically ventilated patients with severe COVID-19 ARDS. Secondary outcomes were the effects of the combined use of APRV and prone positioning on the length of stay and mortality.

Statistical Analysis

All categorical variables were expressed as numbers and percentages, and continuous variables were expressed as median and interquartile ranges. Categorical variables between groups were compared with the chi-square or Fisher's exact test, and continuous variables were compared with the Mann-Whitney U test. A two-tailed *P* value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS (Statistical Package for the Social Sciences Version 24, IBM Corp., Armonk, N.Y., USA).

Results

General Characteristics

A total of 40 patients admitted to the ICU with COVID-19 were included in the study (Figure 1). All patients were mechanically ventilated and required at least one intervention of proning. The numbers of patients who completed the first, second, and third prone were 40, 25, and 15, respectively. Of the 40 patients, 27 (67.5%) were male and the median age of the study population was 65.0 (57.3-72.0 years; Table 1). A total of 23 patients were ventilated with APRV and 17 patients were ventilated with controlled modes. In the controlled mode group, 10 patients were ventilated in volume-controlled mode and 7 patients in pressure-controlled mode. Demographic factors, disease severity scores, and the PaO_2/FiO_2 ratio at admission and before intubation was similar in both groups. There was no difference between the groups in time from ICU admission to intubation and time from intubation to the onset of prone episodes. The time from ICU admission to intubation was 34.0 (6.0-99.0) hours. During this period before intubation, the most appropriate interventions including NIV, high-flow nasal oxygen, and awake-proning interventions were applied to the patients. After intubation, the duration of prone periods was similar between the two groups. D-dimer levels were lower in the APRV group than in the controlled mode group [1.37 (0.70-2.22)] vs. 3.60 (1.08-15.28) g mL^{-1}, respectively, P=0.042). Other laboratory parameters were similar between the two groups.

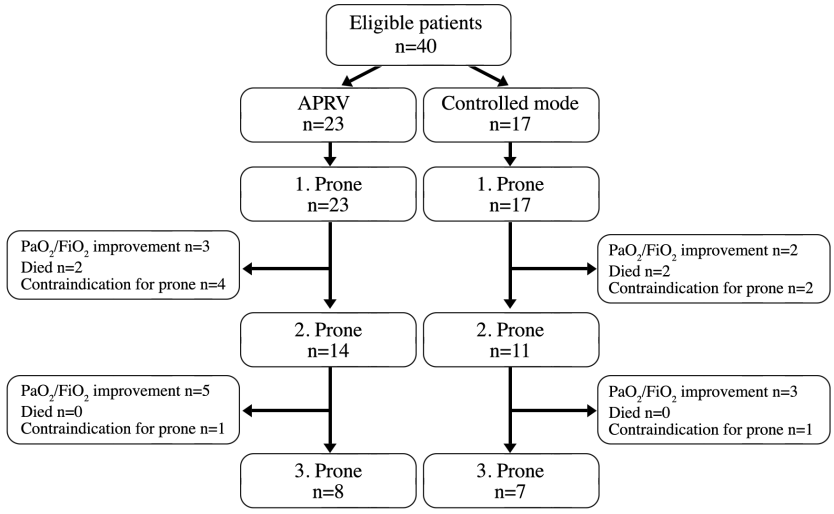

Figure 1. Flowchart of the study population.

APRV, airway pressure release ventilation.

Table 1. Demographic and Clinical Characteristics of Patients (Univariate Analysis)				
Characteristics	**All cases**	**APRV group**	**Controlled mode group**	***P* value**
	(n = 40)	(n = 23)	(n = 17)	
Age, years	65.0 (57.3-72.0)	61.0 (57.0-68.0)	68.0 (62.5-75.5)	0.075
Gender				
Female	13 (32.5)	7 (30.4)	6 (35.3)	1,000
Male	27 (67.5)	16 (69.6)	11 (64.7)	
Body mass index, kg m2^{-1}	27.0 (25.8-30.4)	26.6 (25.9-30.1)	27.0 (25.4-31.9)	0.315
Smoking history	6 (15.0)	2 (8.7)	4 (23.5)	0.373
Comorbidities				
Hypertension	20 (50.0)	11 (47.8)	9 (52.9)	1,000
Diabetes mellitus	13 (32.5)	6 (26.1)	7 (41.2)	0.496
Coronary artery disease	6 (15.0)	3 (13.0)	3 (17.6)	1,000
Congestive heart failure	2 (5.0)	1 (4.3)	1 (5.9)	1,000
Chronic kidney disease	4 (10.0)	2 (8.7)	2 (11.8)	1,000
Dementia	3 (7.5)	1 (4.3)	2 (11.8)	0.565
COPD	3 (7.5)	2 (8.7)	1 (5.9)	1,000
Malignancy	3 (7.5)	2 (8.7)	1 (5.9)	1,000
APACHE II	18.5 (12.3-24.0)	16.0 (13.0-23.0)	20.0 (11.5-25.5)	0.432
SOFA[1]	4.0 (3.0-6.8)	4.0 (3.0-7.0)	4.0 (3.0-6.0)	0.914
CCI	3.0 (1.0-4.8)	3.0 (1.0-5.0)	3.0 (2.0-4.5)	0.607
Laboratory values[2]				
Creatinine, mg dL^{-1}	0.95 (0.71-1.32)	0.91 (0.72-1.26)	0.99 (0.65-1.35)	0.957
Albumin, g dL^{-1}	3.02 (2.77-3.25)	3.04 (2.92-3.26)	2.88 (2.66-3.22)	0.095
ALT, U L^{-1}	61.0 (40.3-87.3)	30.0 (23.0-49.0)	37.0 (27.5-56.5)	0.432
LDH, U L^{-1}	715 (513-881)	533 (487-955)	736 (635-844)	0.290
Ferritin ng mL^{-1}	670 (368-1122)	705 (280-1182)	543 (378-986)	0.705
HS-Troponin I, ng L^{-1}	24.0 (13.4-83.0)	24.0 (11.8-53.8)	24.5 (14.0-491.0)	0.267
D-dimer, µg mL^{-1}	1.65 (0.99-5.45)	1.37 (0.70-2.22)	3.60 (1.08-15.28)	**0.042**
CRP, mg L^{-1}	168 (122-216)	166 (123-216)	184 (100-221)	0.914
Procalcitonin, ng mL^{-1}	0.33 (0.15-1.13)	0.60 (0.11-1.37)	0.28 (0.16-0.70)	0.626
WBC, x 10^{3} µL^{-1}	11.8 (8.3-16.5)	11.6 (8.1-15.8)	14.9 (8.4-18.1)	0.371
Lymphocyte, x 10^{3} µL^{-1}	0.5 (0.3-0.8)	0.4 (0.2-0.7)	0.5 (0.4-1.0)	0.201
Hemoglobin, g dL^{-1}	13.2 (12.1-14.3)	13.1 (12.0-14.8)	13.5 (12.6-14.2)	0.705
Arterial blood gas analysis (at the time of ICU admission)				
pH	7.45 (7.40-7.49)	7.45 (7.40-7.49)	7.45 (7.35-7.49)	0.516
PaO_2, mmHg	54.0 (46.3-69.8)	54.0 (43.0-70.0)	54.0 (48.0-66.2)	1,000
$PaCO_2$, mmHg	32.8 (28.0-37.0)	32.6 (28.0-37.0)	33.0 (28.7-41.5)	0.481
HCO_3, mmol L^{-1}	23.3 (21.0-26.0)	23.3 (21.0-26.0)	24.0 (18.9-26.0)	0.725
PaO_2/FiO_2, mmHg	90.0 (78.5-122.8)	90.0 (78.0-124.0)	90.0 (80.0-119.5)	0.902
Arterial blood gas analysis (before intubation)				
pH	7.38 (7.24-7.48)	7.43 (7.30-7.48)	7.33 (7.17-7.50)	0.386
PaO_2, mmHg	60.0 (51.0-67.5)	62.0 (51.0-70.0)	60.0 (51.5-61.5)	0.481
$PaCO_2$, mmHg	35.5 (32.7-48.8)	35.0 (32.6-40.5)	36.0 (30.5-54.0)	0.978
HCO_3, mmol L^{-1}	24.0 (19.0-27.0)	24.0 (21.0-26.7)	23.0 (16.5-28.4)	0.766
PaO_2/FiO_2, mmHg	96.5 (69.5-112.0)	95.0 (66.0-115.0)	98.0 (72.0-108.5)	0.880

Table 1. Continued

Characteristics	All cases	APRV group	Controlled mode group	*P* value
Prone characteristics				
Time from ICU admission to intubation, (h)	34.0 (6.0-99.0)	44.0 (6.0-95.0)	11.0 (5.0-110.0)	0.665
Time from intubation to APRV initation, (h)	2.0 (1.0-2.0)	2.0 (1.0-2.0)	N/A	N/A
Time from intubation to first prone, (h)	5.5 (3.0-24.0)	7.0 (3.0-32.0)	4.0 (2.0-18.5)	0.206
Time from intubation to second prone, (h)	34.0 (28.0-56.0)	44.0 (28.8-90.0)	31.0 (28.0-44.0)	0.153
Time from intubation to third prone, (h)	77.0 (52.0-96.0)	84.5 (52.8-150.0)	63.0 (51.0-86.0)	0.297
Duration of 1. prone, (h)	16.5 (14.3-18.0)	16.0 (14.0-18.0)	17.0 (14.5-19.0)	0.544
Duration of 2. prone, (h)	16.0 (15.0-17.0)	16.0 (14.8-16.3)	17.0 (15.0-19.0)	0.177
Duration of 3. prone, (h)	14.0 (8.0-17.0)	15.0 (12.3-17.0)	10.0 (6.0-16.0)	0.352

All values are expressed as numbers (percentages) or median (interquartile range). Statistically significant values are expressed in bold.

APACHE II, acute physiology and chronic health evaluation II; APRV, airway pressure release ventilation; ALT, alanine transaminase; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; FiO_2, fraction of inspired oxygen; HS Troponin I, high-sensitive troponin I; ICU, intensive care unit; LDH, lactate dehydrogenase; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; SOFA score, the sequential organ failure assessment score; WBC, white blood cell count.

[1]Calculated on the day of ICU admission.

[2]Tested on the day of ICU admission.

Table 2. Characteristics Before and After 1. Prone Position

Characteristics	Before prone (within 1 h)			After prone (within 1 h)		
	APRV (n = 23)	Controlled mode (n = 17)	*P* value	APRV (n = 23)	Controlled mode (n = 17)	*P* value
Mechanical ventilation parameters						
P high (APRV)	25.0 (23.0-28.0)	N/A	N/A	25.0 (23.0-26.0)	N/A	N/A
P low (APRV)	3.0 (2.0-4.0)	N/A	N/A	3.0 (2.9-4.0)	N/A	N/A
PC/PS (controlled mode)	N/A	20.0 (12.0-20.5)	N/A	N/A	18.0 (16.0-24.0)	N/A
PEEP (controlled mode)	N/A	8.0 (6.0-11.0)	N/A	N/A	9.0 (6.0-10.0)	N/A
P peak	25.0 (24.0-29.0)	27.0 (23.0-31.0)	0.59	25.0 (24.0-29.0)	28.0 (25.5-31.5)	0.06
P mean	21.0 (19.0-24.0)	15.0 (12.0-16.0)	**<0.001**	20.0 (19.0-23.0)	15.0 (12.0-17.5)	**<0.001**
PEEP (controlled mode)	N/A	8.0 (6.0-11.0)	N/A	N/A	9.0 (6.0-10.0)	N/A
Minute ventilation	6.4 (5.6-8.0)	7.9 (6.4-9.6)	**0.014**	6.5 (5.7-8.6)	8.3 (7.5-9.0)	**0.002**
Cdyn	32.0 (23.0-38.1)	26.0 (18.9-40.5)	0.315	35.7 (23.0-43.0)	36.0 (20.5-42.0)	0.588
R	13.0 (9.8-16.7)	14.0 (11.3-16.0)	0.685	14.0 (12.0-15.0)	14.0 (11.3-18.0)	0.516
ETT diameter, mm	8.00 (8.00-8.00)	8.00 (7.75-8.00)	0.787	8.00 (8.00-8.00)	8.00 (7.75-8.00)	0.787
Arterial blood gas analysis						
pH	7.38 (7.29-7.44)	7.31 (7.23-7.38)	**0.010**	7.35 (7.28-7.41)	7.36 (7.29-7.38)	0.957
$PaCO_2$, mmHg	40.7 (37.2-53.0)	60.0 (42.0-64.0)	**0.015**	46.0 (41.0-55.4)	58.0 (44.5-62.5)	0.101
HCO_3, mmol L^{-1}	24.0 (22.0-26.6)	23.0 (20.4-27.9)	0.551	24.2 (20.7-27.5)	25.0 (20.5-29.1)	0.705
SaO_2, %	88 (80-92)	88 (84-93)	0.745	96 (93-97)	95 (90-96)	0.290
PaO_2, mmHg	57 (50-68)	61 (57-74)	0.173	87 (71-104)	76 (64-87)	0.201
PaO_2/FiO_2, mmHg	87 (73-113)	98 (82-119)	0.193	155 (125-185)	132 (110-150)	0.151

All values are expressed as numbers (percentages) or median (interquartile range). Statistically significant values are expressed in bold.

APRV, airway pressure release ventilation; Cdyn, dynamic compliance; ETT, endotracheal tube; FiO_2, raction of inspired oxygen; N/A, not applicable; P, pressure; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; PEEP, positive end-expiratory pressure; R, resistance; SO_2, arterial oxygen saturation.

The Characteristics of the 1. Prone

Of the 40 patients in the first prone position, 23 were ventilated with APRV and 17 were ventilated with a controlled mode (Table 2).

In patients ventilated with APRV, the median (interquartile range) of the PaO_2/FiO_2 ratio before the first prone was not different when compared with patients ventilated with controlled modes [87 (73-113)] vs. 98 (82-119)] mmHg, respectively, *P*=0.193). After the first prone, the PaO_2/FiO_2 ratio of the APRV group was higher compared to the PaO_2/FiO_2 ratio of the controlled mode group, but it was not statistically significant [155 (125-185)] vs. 132 (110-150) mmHg, respectively, *P*=0.151).

The Characteristics of the 2. Prone

Two patients in the APRV group and two patients in the controlled mode group died at follow-up after the first prone period. The physicians did not require the second prone position because the PaO_2/FiO_2 ratio improved for three patients in the APRV group and for two patients in the controlled mode group after the first prone. The second prone was not applied to four patients in the APRV group and to two patients in the controlled mode group because of hemodynamic instability. Of the 25 patients in the second prone position, 14 were ventilated with APRV and 11 were ventilated in the controlled mode.

Before the second prone, the PaO_2/FiO_2 ratio was 136 (96-171) mmHg in the APRV group and 123 (77-147) mmHg in the controlled mode group (*P*=0.149; Table 3). After the second prone, the PaO_2/FiO_2 ratio of the APRV group was higher compared to the PaO_2/FiO_2 ratio of the controlled mode group [189 (150-237)] vs. 127 (100-146) mmHg, respectively, *P*=0.025).

Characteristics of the Third Prone

The physicians did not require the third prone position because the PaO_2/FiO_2 ratio improved following the second prone position for five patients in the APRV group and for three patients in the controlled mode group. The third prone was not applied to one patient in the APRV group and one

Table 3. Characteristics Before and After 2. Prone Position

Characteristics	Before prone (within 1 h)			After prone (within 1 h)		
	APRV (n = 14)	Controlled mode (n = 11)	*P* value	APRV (n = 14)	Controlled mode (n = 11)	*P* value
Mechanical ventilation parameters						
P high (APRV)	22.5 (22.0-28.0)	N/A	N/A	22.5 (22.0-26.5)	N/A	N/A
P low (APRV)	3.0 (2.5-3.3)	N/A	N/A	3.2 (2.5-4.0)	N/A	N/A
PC/PS (controlled mode)	N/A	20.0 (14.0-22.0)	N/A	N/A	18.0 (14.0-23.0)	N/A
PEEP (controlled mode)	N/A	10.0 (7.0-12.0)	N/A	N/A	9.0 (6.0-10.0)	N/A
P peak	26.0 (22.0-28.0)	30.0 (24.0-33.0)	**0.03**	24.0 (22.0-26.5)	28.0 (24.0-35.0)	**0.04**
P mean	20.0 (18.7-25.0)	14.0 (11.0-17.0)	**<0.001**	20.0 (18.0-22.7)	16.0 (12.0-18.0)	**<0.001**
PEEP (controlled mode)	N/A	10.0 (7.0-12.0)	N/A	N/A	9.0 (6.0-10.0)	N/A
Minute ventilation	6.6 (5.7-8.3)	8.6 (7.3-9.8)	**0.021**	6.8 (5.8-9.7)	8.0 (6.9-8.5)	0.317
Cdyn	29.7 (19.5-40.8)	25.0 (16.9-45.0)	0.647	38.9 (25.9-54.5)	34.0 (30.0-48.0)	0.851
R	12.5 (10.8-15.3)	15.0 (12.0-17.2)	0.373	13.7 (9.9-16.2)	15.0 (14.0-17.3)	0.095
ETT diameter, mm	8.00 (7.50-8.00)	8.00 (8.00-8.00)	0.077	8.00 (7.50-8.00)	8.00 (8.00-8.00)	0.077
Arterial blood gas analysis						
pH	7.37 (7.30-7.41)	7.35 (7.31-7.38)	0.727	7.36 (7.32-7.44)	7.29 (7.22-7.38)	0.120
$PaCO_2$, mmHg	48.1 (41.0-55.0)	52.0 (46.0-63.0)	0.267	48.6 (43.2-52.1)	61.0 (44.0-95.0)	0.085
HCO_3, mmol L^{-1}	24.7 (22.0-30.5)	27.0 (24.0-28.0)	0.609	28.0 (23.0-32.3)	27.0 (24.0-33.0)	0.979
SaO_2, %	95 (93-96)	93 (84-97)	0.222	97 (96-97)	94 (90-97)	0.085
PaO_2, mmHg	79 (61-85)	72 (51-88)	0.434	96 (78-110)	70 (61-102)	0.107
PaO_2/FiO_2, mmHg	136 (96-171)	123 (77-147)	0.149	189 (150-237)	127 (100-146)	**0.025**

All values are expressed as numbers (percentages) or median (interquartile range). Statistically significant values are expressed in bold.

APRV, airway pressure release ventilation; Cdyn, dynamic compliance; ETT, endotracheal tube; FiO_2, fraction of inspired oxygen; N/A, not applicable; P, pressure; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; PEEP, positive end-expiratory pressure; R, resistance, SO_2, arterial oxygen saturation.

patient in the controlled mode group due to hemodynamic instability. Of the 15 patients in the second prone position, 8 were ventilated with APRV and 7 were ventilated with the controlled mode.

Before the third prone, the PaO_2/FiO_2 ratio was 132 (81-177) mmHg in the APRV group and 95 (57-102) mmHg in the controlled mode group (*P*=0.024; Table 4). After the third prone, the PaO_2/FiO_2 ratio of the APRV group was higher compared to the PaO_2/FiO_2 ratio of the controlled mode group [194 (132-263)] vs. 83 (71-136) mmHg, respectively, *P*=0.021). The change in the PaO_2/FiO_2 ratio over time is presented in Figure 2.

Major Events and Complications During the Prone Position and During ICU Stay

There was no difference between the two groups in major events or complications associated with prone positions (Table 5).

Spontaneous subcutaneous emphysema was detected in two patients in the pre-intubation follow-up. After intubation,

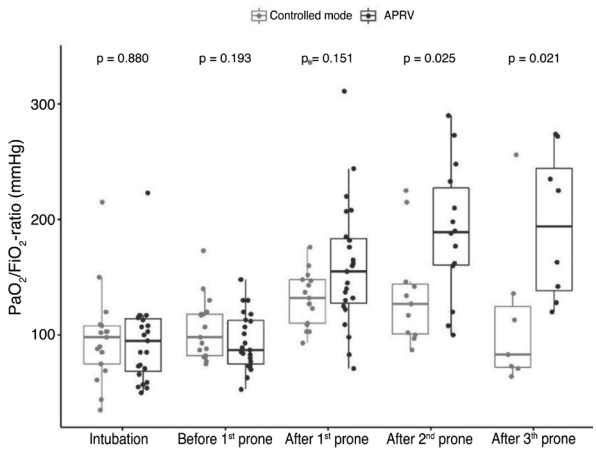

Figure 2. Median (interquartile range) of the PaO_2/FiO_2 ratio (mmHg) before the intubation and during the prone positioning in the study groups.

APRV, airway pressure release ventilation; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen.

Table 4. Characteristics Before and After 3. Prone Position

Characteristics	Before prone (within 1 h)			After prone (within 1 h)		
	APRV (n = 8)	Controlled mode (n = 7)	*P* value	APRV (n = 8)	Controlled mode (n = 7)	*P* value
Mechanical ventilation parameters						
P high (APRV)	26.0 (20.0-28.5)	N/A	N/A	26.0 (21.0-27.5)	N/A	N/A
P low (APRV)	3.1 (2.1-4.0)	N/A	N/A	3.6 (2.3-4.0)	N/A	N/A
PC/PS (controlled mode)	N/A	18.0 (14.0-25.0)	N/A	N/A	18.0 (14.0-24.0)	N/A
PEEP (controlled mode)	N/A	10.0 (9.0-10.0)	N/A	N/A	10.0 (8.0-11.0)	N/A
P peak	26.0 (22.0-29.8)	33.0 (24.0-39.0)	0.15	26.0 (21.3-27.8)	33.0 (25.0-35.0)	0.23
P mean	21.0 (17.2-23.8)	17.0 (14.0-18.0)	**0.04**	21.0 (18.0-23.5)	16.0 (15.0-18.0)	0.05
PEEP (controlled mode)	N/A	10.0 (9.0-10.0)	N/A	N/A	10.0 (8.0-11.0)	N/A
Minute ventilation	7.5 (5.6-11.6)	7.9 (7.1-9.5)	0.867	7.1 (5.7-9.5)	7.5 (5.9-8.1)	1,000
Cdyn	31.5 (24.5-39.7)	26.4 (17.0-54.0)	0.779	33.5 (22.2-47.4)	30.0 (18.0-72.0)	0.867
R	15.2 (7.1-20.7)	12.0 (9.6-15.9)	1.000	14.4 (9.5-16.6)	15.0 (12.9-19.8)	0.536
ETT diameter, mm	8.00 (7.50-8.00)	8.00 (8.00-8.00)	0.188	8.00 (7.50-8.00)	8.00 (8.00-8.00)	0.188
Arterial blood gas analysis						
pH	7.36 (7.29-7.44)	7.34 (7.23-7.41)	0.613	7.41 (7.24-7.47)	7.20 (6.9-7.4)	0.054
$PaCO_2$, mmHg	50.0 (43.0-66.8)	52.0 (46.0-62.0)	0.779	53.6 (44.5-57.2)	67.0 (55.0-104.0)	**0.029**
HCO_3, mmol L^{-1}	29.0 (24.3-33.1)	30.0 (20.0-35.4)	0.955	27.5 (21.2-32.5)	29.0 (13.7-31.0)	0.867
SaO_2, %	94 (87-98)	88 (75-92)	0.054	97 (92-98)	84 (82-92)	**0.040**
PaO_2, mmHg	66 (54-77)	51 (40-58)	0.094	92 (67-127)	51 (50-82)	0.054
PaO_2/FiO_2, mmHg	132 (81-177)	95 (57-102)	**0.024**	194 (132-263)	83 (71-136)	**0.021**

All values are expressed as numbers (percentages) or median (interquartile range). Statistically significant values are expressed in bold.

APRV, airway pressure release ventilation; Cdyn, dynamic compliance; ETT, endotracheal tube; FiO_2, fraction of inspired oxygen; N/A, not applicable; P, pressure; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; PEEP, positive end-expiratory pressure; R, resistance; SO_2, arterial oxygen saturation.

Table 5. Outcomes (Univariate Analysis)				
Characteristics	**All cases**	**APRV**	**Controlled mode**	***P* value**
	(n = 40)	**(n = 23)**	**(n = 17)**	
NMBA use during prone, n (%)				
First prone	4 (10.0)	0 (0)	4 (23.5)	**0.026**
Second prone	3 (7.5)	0 (0)	3 (27.3)	0.072
Third prone	2 (5.0)	1 (12.5)	1 (14.3)	1,000
Events/complications during prone positioning				
New-onset or increased need for vasopressors	10 (25.0)	4 (17.4)	6 (35.3)	0.274
Pressure ulcer	8 (20.0)	3 (13.0)	5 (29.4)	0.250
Oliguria/anuria	5 (12.5)	2 (8.7)	3 (17.6)	0.634
Arrhythmia	4 (10.0)	2 (8.7)	2 (11.8)	1,000
Catheter complications	1 (2.5)	0 (0)	1 (5.9)	0.425
Corneal abrasion	1 (2.5)	0 (0)	1 (5.9)	0.425
Events/therapies during ICU stay				
Need for any dose of vasopressors, n (%)	33 (82.5)	19 (82.6)	14 (82.4)	1,000
Number of vasopressor days	6.0 (2.0-8.0)	7.0 (2.0-9.0)	5.0 (1.5-8.0)	0.516
ICU-acquired infections	31 (77.5)	18 (78.3)	13 (76.5)	1,000
Acute kidney injury	22 (55.0)	12 (52.2)	10 (58.8)	0.755
Renal replacement therapy	14 (35.0)	9 (39.1)	5 (29.4)	0.739
Spontaneous subcutaneous emphysema/pneumomediastinum	2 (5.0)	1 (4.3)	1 (5.9)	1,000
Barotrauma events after IMV	5 (12.5)	3 (13.0)	2 (11.8)	1,000
Chest tube requirement	2 (5.0)	1 (4.3)	1 (5.9)	1,000
Treatment for COVID-19				
Favipiravir	40 (100.0)	23 (100.0)	17 (100.0)	N/A
LMWH	40 (100.0)	23 (100.0)	17 (100.0)	N/A
ASA	38 (95.0)	22 (95.7)	16 (94.1)	1,000
Dipyridamole	38 (95.0)	22 (95.7)	16 (94.1)	1,000
Corticosteroids	38 (95.0)	22 (95.7)	16 (94.1)	1,000
Pulse corticosteroid*	33 (82.5)	17 (73.9)	16 (94.1)	0.205
Tocilizumab	6 (15.0)	3 (13.0)	3 (17.6)	1,000
Duration of IMV (days)	10.0 (6.0-15.0)	11.0 (7.0-15.0)	7.0 (5.0-23.0)	0.411
Duration of APRV (days)	3.0 (0.0-7.0)	7.0 (3.0-10.0)	N/A	N/A
ICU length of stay (days)	14.0 (10.3-17.0)	14.0 (11.0-17.0)	13.0 (7.5-24.0)	0.467
ICU mortality	35 (87.5)	19 (82.6)	16 (94.1)	0.373
Hospital mortality	35 (87.5)	19 (82.6)	16 (94.1)	0.373
28-day mortality**	29 (72.5)	17 (73.9)	12 (70.6)	1,000

All values are expressed as numbers (percentages) or median (interquartile range). Statistically significant values are expressed in bold.

APRV, airway pressure release ventilation; ASA, acetylsalicylic acid; ICU, intensive care unit; IMV, invasive mechanical ventilation; LMWH, low molecular weight heparin; NMBA, neuromuscular blocking agents.

*Intravenous injection, 250 mg day for 3 days,

**Six patients died after the period of 28-day follow-up. These patients died because of secondary events. The median follow-up of these six patients was 35.5 (29.8-54.0) days.

one was ventilated with the controlled mode and the other with APRV. Emphysema did not worsen after IMV in both patients. Barotrauma events, including new subcutaneous emphysema, pneumomediastinum, pneumopericardium, or pneumothorax, were detected in 5 (12.5%) patients. One patient in the APRV group and one patient in the controlled mode group required a chest tube after barotrauma. The incidence of barotrauma events were not different in the APRV group and in the controlled mode group (13.0% vs. 11.8%, respectively; *P*=1000).

One of two patients with spontaneous subcutaneous emphysema survived. All 5 patients with barotrauma died.

ICU Length of Stay and 28-day Mortality

The length of stay in the ICU was similar in both groups. The 28-day mortality was 73.9% in the APRV group and 70.6% in the controlled mode group (*P*=1000).

Discussion

This prospective study addressed the possible combined effect of APRV and prone positioning on the improvement of oxygenation in patients with severe COVID-19, and obtained three important results. Firstly, when combining prone positioning with APRV, improvement in oxygenation was better than with the controlled mode, especially in the second and third prone positions. Secondly, APRV can be safely used in COVID-19 ARDS patients because barotrauma events are similar in both groups. Thirdly, APRV did not reduce mortality more than controlled modes in COVID-19 patients with ARDS.

To our knowledge, research on combined APRV and prone positioning is limited to one randomized clinical trial,[20] and a retrospective study of patients with severe 2009 pandemic influenza A (H1N1) pneumonia.[21] In the randomized controlled trial, 33 patients with acute lung injury who required the prone position were ventilated with either synchronized intermittant mandatory ventilation (SIMV) or APRV. They found that the PaO_2/FiO_2 ratio of the APRV group was greater than that of the SIMV group after the second prone [82 (37.0-141.0)] and 50 (24.0-68.0) mmHg, *P*=0.02, respectively. However, serious complications and 28-day mortality were similar in both groups in the randomized controlled trials.[20] In a retrospective study of patients with ARDS associated with 2009 pandemic influenza A (H1N1), 11 of 14 mechanically ventilated patients had refractory hypoxemia despite APRV administration. Maintenance of APRV and following proving improved hypoxemia in these patients.[21] Likewise, the positive effect of combined APRV ventilation and proning on the improvement of oxygenation have been demonstrated in a case series.[22] Our findings were similar to the literature. In this study, after the first prone period, the PaO_2/FiO_2 ratio was higher in the APRV group than in the controlled mode group but was not statistically significant. After the second prone period, the PaO_2/FiO_2 ratio was significantly higher in the APRV group than in the controlled mode group, and this significance was maintained after the third prone position.

In a historical-comparative study, barotrauma was detected in 15% (n = 89) of 601 COVID-ARDS patients, while barotrauma was detected in 10% (n = 28) of 285 patients with non-COVID-ARDS in the same center in previous years.[23] In another study of 20 mechanically ventilated patients with COVID-19, barotrauma events were detected in 8 (40%) patients.[24] Not only the result of barotrauma but also spontaneous subcutaneous emphysema or pneumomediastinum/pneumothorax was detected in COVID-19 patients.[25,26] High barotrauma events and cases of spontaneous pneumomediastinum/pneumothorax in COVID-19 patients raise questions about whether COVID-19 infection uniquely increases risk. In our study, we detected two patients with spontaneous subcutaneous emphysema at follow-up before IMV administration. Barotrauma events had a similar rate with literature in mechanically ventilated patients in our study. Barotrauma was an independent risk factor for death in mechanically ventilated COVID-19 patients.[23] Similarly, in this study, all five patients with barotrauma died.

In a meta-analysis, including 57,420 adult patients with COVID-19 who received IMV, the overall reported case fatality rate (CFR) was estimated as 45% [95% confidence interval (CI), 39-52%].[27] In this meta-analysis, among studies in which age-stratified CFR was available, pooled CFR estimates were 84.4% (95% CI, 83.3-85.4%) in patients with age above 80 years.[27] In previous studies, high mortality rates were reported in patients undergoing IMV.[28] Similarly, 28-day mortality was 72.5% (n = 29) in our specific study of patients with ARDS who underwent IMV and proning.

Limitations and Strengths of the Study

The limitations of the study are as follows: (1) Although care was taken to maintain spontaneous breathing in the APRV group, in rare cases, patients required temporary deep sedation due to prone position intolerance; (2) We did not correlate plateau pressures between groups during prone positioning because it was not possible to measure in APRV ventilation; (3) The sample size was small. On the other hand, our study had several strengths. This study was conducted on a homogenous population that included patients with ARDS. The factors affecting oxygenation were similar in both groups. This homogeneity can make comparisons between groups more clear.

Conclusion

Prone positioning and APRV ventilation have advantageous synergistic effects on oxygenation without increasing complications in patients with COVID-19 ARDS. This

combination can be considered rescue therapy in refractory hypoxemia in this group of patients. However, improvement in oxygenation did not benefit mortality. The effect of APRV ventilation and proning on mortality in COVID-19 ARDS need to be investigated in larger studies.

Ethics Committee Approval: This study was approved by of Dokuz Eylül University Non-Invasive Research Ethics Committee (approval no: 2021/03-18, date: 01.02.2021).

Informed Consent: The eligible patients were informed about the study during the preoperative evaluation and their written consents were obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.E., M.N.Y., M.K., E.Y., Be.E., A.N.G.; Design - B.E., M.N.Y., M.K., E.Y., Be.E., A.N.G.; Supervision - E.Y., Be.E., A.N.G.; Materials - B.E., M.N.Y., M.K., N.B., Be.E., A.N.G.; Data Collection and/or Processing - B.E., M.N.Y., M.K., N.B.; Analysis and/or Interpretation - B.E., M.N.Y., M.K., A.N.E., Be.E.; Literature Review - B.E., E.Y., Be.E., A.N.G.; Writing - B.E., M.N.Y., M.K., A.N.E., E.Y., Be.E., A.N.G.; Critical Review - E.Y., Be.E., A.N.G.

Declaration of Interests: The authors have no conflict of interest to declare.

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