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ORIGINAL INVESTIGATION

The effect of preemptive airway pressure release ventilation on patients with high risk for acute respiratory distress syndrome: a randomized controlled trial☆

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KEYWORDS
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Ventilation modes

Abstract
Background and objectives: The objective of this study was to investigate the use of early APRV mode as a lung protective strategy compared to conventional methods with regard to ARDS development.
Methods: The study was designed as a randomized, non-blinded, single-center, superiority trial with two parallel groups and a primary endpoint of ARDS development. Patients under invasive mechanical ventilation who were not diagnosed with ARDS and had Lung Injury Prediction Score greater than 7 were included in the study. The patients were assigned to APRV and P-SIMV + PS mode groups.
Results: Patients were treated with P-SIMV+PS or APRV mode; 33 (50.8%) and 32 (49.2%), respectively. The P/F ratio values were higher in the APRV group on day 3 (p = 0.032). The fraction of inspired oxygen value was lower in the APRV group at day 7 (p = 0.011).While 5 of the 33

☆ The study was performed in a general intensive care unit with 18 bed capacity in Samsun Ondokuz Mayıs University, Hospital of School of Medicine, Intensive Care Unit, Samsun, Turkey.

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patients (15.2%) in the P-SIMV+PS group developed ARDS, one out of the 32 patients (3.1%) in the APRV group developed ARDS during follow-up (p = 0.197). The groups didn't differ in terms of vasopressor/inotrope requirement, successful extubation rates, and/or mortality rates (p = 1.000, p = 0.911, p = 0.705, respectively). Duration of intensive care unit stay was 8 (2–11) days in the APRV group and 13 (8–81) days in the P-SIMV+PS group (p = 0.019).
Conclusions: The APRV mode can be used safely in selected groups of surgical and medical patients while preserving spontaneous respiration to a make benefit of its lung-protective effects. In comparison to the conventional mode, it is associated with improved oxygenation, higher mean airway pressures, and shorter intensive care unit stay. However, it does not reduce the sedation requirement, ARDS development, or mortality.

Introduction

Airway pressure release ventilation (APRV) is a mode of mechanical ventilation that alternates between two levels of continuous positive airway pressure (CPAP) support. Additionally, it allows spontaneous respiratory effort at either CPAP level.[1] It is considered as an alternative, life-saving modality in patients with acute respiratory distress syndrome (ARDS) that struggle for oxygenation.[2] Compared to the classical ventilation, APRV has been shown to provide lower peak pressure, better oxygenation, less circulatory loss, and better gas exchange without deteriorating the hemodynamic condition of the ARDS patient.[3] This mode is believed to help to achieve the target of opening consolidated lung areas (recruitment) and to prevent repeated opening-closing of alveoli (decruitment). However, there is still insufficient and limited proof to support this hypothesis.

Recently, it has been proposed that the early use of protective mechanical ventilation with APRV could be used preemptively to prevent the development of ARDS in high risk patients.[4–8] In that study, APRV prevented clinical and histological lung injury by protecting alveolar epithelial integrity, preserving surfactant and alveolar stability, and reducing pulmonary edema.[6]

The primary purpose of the present study was to investigate the early use of APRV as a lung-protecting strategy compared to the conventionally used methods in a patient population with high risk of ARDS.

Methods

The CONSORT guideline was used as a guide for this manuscript. Our study was carried out in Ondokuz Mayıs University in the 3rd level intensive care unit patients. This study was planned as a single-centered, prospective, and randomized-controlled study in a general intensive care unit with an 18-bed capacity. The majority of the general patient population is made up of trauma and postoperative patients. The local ethics committee reviewed and approved the study protocol (protocol number: 2016/175) prior to the start of the investigation. The study was also registered on the ClinicalTrials with protocol nº NCT04699513. Enrollment for the study was performed from May 2016 to October 2018. Written informed consent was obtained from a relative of each patient.

Study design and sample

The study included patients who required invasive mechanical ventilation but was not initially diagnosed with ARDS[9]; had a LIPS (Lung Injury Prediction Score) greater than 7[10]; and stayed in the Intensive Care Unit (ICU) for more than 24 hours. Patient demographic properties, sedation requirements, inotrope/vasopressor levels, ARDS development status, length of ICU and hospital stay, and mechanical ventilation related parameters were recorded. Exclusion criteria were pregnancy, intracranial hypertension (suspected or confirmed by measurement with external ventricular drainage catheter), severe chronic obstructive pulmonary disease or type II respiratory failure, confirmed bronchopleural fistula, documented barotrauma, history of pneumonectomy, and age below 18 or above 85 years. Consecutive eligible patients were enrolled by block randomization with a 1:1 allocation ratio and randomly assigned to the APRV or the Pressure controlled Synchronized Intermittent Mandatory Ventilation + Pressure Support (P-SIMV+PS) groups using opaque, sealed envelopes.

Ventilator settings

All mechanical ventilation settings were made by intensivists or trained residents on the night shifts. Prior to randomization, all patients were treated with VC-SIMV mode. Patients admitted during the day were ventilated in VC-SIMV mode until the main investigators evaluated the patient (1–2 hours). The patient was admitted in the evening-night shift were ventilated in VC-SIMV mode until the main investigators took over the shift in the morning (maximum 16 hours). Assignment to groups was performed following the calculation of the LIPS score. Microprocessor-controlled mechanical ventilators (Galileo GOLD; Hamilton Medical AG, Bonaduz, Switzerland) and heated humidifiers were used as a standard for all patients. In both groups, mechanical ventilation targets were determined as maintaining plateau airway pressure (P_{plateu}) < 30 cmH_2O and PaO_2 between 60–100 mmHg or SO_2 > 88%. In both groups, arte-

Table 1 Comparison of demographics.

Parameter		P-SIMV+PS	APRV	*p*
Demographic				
Sex[a]	Female	4 (33.33)	8 (66.67)	
	Male	29 (54.72)	24 (45.28)	0.309
BMI[a]	< 30	29 (54.72)	24 (45.28)	
	> 30	4 (33.33)	8 (66.67)	0.309
Diagnosis				
Surgical/Trauma[a]				
	Intracranial	13 (61.9)	8 (38.1)	
	Intra-abdominal	2 (66.67)	1 (33.33)	
	Orthopedic	1 (20)	4 (80)	
	Thoracic	6 (50)	6 (50)	
	Spinal Cord	0 (0)	2 (100)	
	Other	3 (60)	2 (40)	
Surgical/Non-trauma[a]				
	Intra-abdominal	5 (62.5)	3 (37.5)	
	Other	1 (100)	0 (0)	
Medical[a]				
	Pulmonary	1 (25)	3 (75)	
	Intra-abdominal	0 (0)	1 (100)	
	Other	1 (33.33)	2 (66.67)	0.500
Sepsis[a]	No	31 (54.39)	26 (45.61)	
	Yes	2 (25)	6 (75)	0.149
Comorbidity				
Comorbidity[a]	No	19 (47.5)	21 (52.5)	
	Yes	14 (56.0)	11 (44.0)	0.680

BMI, body mass index.
All values are shown as n (%).
[a] Pearson chi-square test, $p < 0.05$.

rial blood gas measurement was performed at least twice a day. Oxygenation and respiratory mechanics were evaluated by comparing the P-SIMV+PS and the APRV groups at baseline and on days 1, 2, 3, and 7. Patients were followed until transfer to CPAP/T-tube and extubation or a maximum of 28 days. During this period, follow-up was terminated once at extubation, exitus, and/or when discharge from ICU or ARDS occurred.

P-SIMV+PS group

The reason behind using P-SIMV+PS as a conventional mode was that it has a pressure-controlled mode similar to the APRV. Pressure level was adjusted in order to get a Vt of 6–8 $ml.kg^{-1}.PBW^{-1}$ (predicted body weight). Optimal Positive End-Expiratory Pressure (PEEP) between 5–10 cmH_2O was applied to all patients by titration according to the O_2 requirement.

The APRV group

Standard initial settings were T_{high}/T_{low}: 4/0.8 seconds, P_{high}: taking $P_{plateau}$ value (if patient is paralyzed) or P_{mean} in the previous conventional method as reference, $P_{plateau}$ < 30 cm H_20 and target Vt 6–8 $mL.kg^{-1}$ PBW^{-1}. P_{low} was always set to 0 cm H_2O. T_{low} was adjusted according to the PCO_2 value in blood gas measurement by evaluating expiratory flow curve (gas flow wave form), and to get a release duration of 10–14/$cycle^{-1}$. T_{low} range was adjusted as 0.4–1.2 seconds.[12,13] Weaning was performed according to the European Respiratory Society Weaning Task Force recommendations in both groups.[14]

Medical and supportive treatments

Fluidic management, antibiotic strategy, glucose control, and enteral nutrition were also standardized between the two groups according to the ICU protocols. The sedation goal was a Richmond Agitation Sedation Scale score of -2 to 0.[15] The sedation doses were not evaluated. None of the patients received neuromuscular blocker.

Statistical analysis

The primary outcome of developing ARDS in the light of P/F ratio[8] (Clinically defined ALI/ARDS developed in the CMV group – mean [SE] PaO2/FIO2 [P/F] ratio, 242.96 [S.E. 24.82]) was prevented with APRV (P/F ratio, 478.00 [S.E.41.38]; $p < 0.05$ vs CMV). The power analysis using the Gpower computer program[11] indicated that a total sample of 58 people would be needed to detect large effects (d: 0.888) with a 90% power using a *t*-test between means with 2-tailed alpha at 0.05.

All data were analyzed using IBM SPSS version 23 (Chicago, USA). The Shapiro Wilk test was used to determine whether the data were normally distributed. Comparisons of data that were not normally distributed were made with the Kruskal Wallis test and the Mann Whitney U test. Categorical data were analyzed with the Pearson chi-square test. The groups were compared with regard to laboratory parameters measured on days 1, 2, 3, and 7. Non-normally distributed data were presented as median (min-max), while normally distributed data were presented as the mean ± standard deviation. Categorical data were expressed as frequency and percentage. A *p*-value of less than 0.05 was considered significant.

Study endpoint

The primary endpoint of the study was to investigate whether early use of APRV as a lung-protecting strategy was superior to the conventional methods in a patient population with high risk of ARDS as determined by the calculation of the LIPS score. The secondary endpoint was to determine whether this mode provided any improvement in oxygenation, airway pressures, sedation requirements, mechanical ventilation time, and length of ICU/hospital stay.

Results

Comparison of demographic and baseline data between patient groups

Sixty-five patients meeting the eligibility criteria were enrolled (Fig. 1). Seven patients were excluded from the study due to being diagnosed with ARDS. During the follow-up, 6 patients developed ARDS; however, their data were included in the baseline evaluation since ARDS occurred after day 7. Thirty-three (50.8%) patients were treated with P-SIMV+PS and 32 (49.2%) patients were treated with APRV. Twelve (18.5%) of the study participants were female and 53 (81.5%) were male. The most common diagnosis among primary ICU admission was general trauma in 48 (73.8%) of the patients. Properties of patients did not differ significantly between the two study groups (Table 1).

The median age and body weight did not differ between the groups (p = 0.509 and p = 0.402, respectively). Baseline LIPS, APACHE II, and SOFA (Sequential Organ Failure Assessment) scores did not show a statistically significant difference between the groups (Table 2).

While 5 of the 33 patients (15.2%) in the P-SIMV+PS group developed ARDS, one of 32 patients (3.1%) in the APRV group developed ARDS during follow-up (p = 0.197).

The groups did not differ in terms of vasopressor/inotrope requirement, successful extubation rates, and mortality rates (p = 1.000, p = 0.911, and p = 0.705, respectively). The mechanical ventilation time was 9 (3–65) days in the P-SIMV+PS group and 7.5 (2–29) days in the APRV group (p = 0.171). The ICU stay length was significantly higher in the P-SIMV+PS group (p = 0.019). Hospital stay length did not differ between the groups (p = 0.242). The comparison of the end points is shown in Table 3.

Table 2 Comparison of baseline properties of P-SIMV+PS and APRV groups.

	P-SIMV+PS	APRV	*p*
Age (year)[a]	54 (18–81)	50 (18–74)	0.590
Weight (kg)[a]	82 (60–110)	80 (23–120)	0.402
LIPS[a]	9 (7–13)	8.5 (7–12)	0.226
APACHE II[a]	17 (7–36)	17 (7–35)	0.509
SOFA[a]	6 (3–19)	7 (3–18)	0.464

LIPS, Lung injury prediction score; APACHE II, Acute Physiology, Age, Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment.
All values are shown as med (min–max).
[a] Mann Whitney U test, $p < 0.05$.

Table 3 Comparison of outcomes of patients according to groups.

Parameter	P-SIMV+PS	APRV	*p*
Sedation	30 (91.0)	23 (71.9)	0.061
Vasopressor/Inotrope[a]	23 (69.7)	23 (71.9)	1.000
ARDS[a]	5 (15.2)	1 (3.1)	0.197
Tracheotomy[a]	5 (15.2)	2 (6.3)	0.427
Extubation[a]	19 (57.6)	17 (53.1)	0.911
Mortality[a]	17 (51.5)	14 (43.8)	0.705

ARDS, acute respiratory distress syndrome.
All values are shown as n (% within the group).
[a] Pearson chi-square test, $p < 0.05$.

Statistics of surviving patients

There was no statistically significant difference between the groups regarding mortality. After excluding 31 patients with mortality, 16 of the remaining 34 surviving patients (47%) were in the P-SIMV+PS group, and 18 (53%) were in the APRV group. There was no difference between the groups regarding mechanical ventilation time or hospital stay length (p = 0.211 and p = 0.297, respectively). The ICU stay length was significantly shorter in the APRV group (p = 0.027) (Table 4).

Comparison of blood gas and mechanical ventilation parameters

The worst of blood gas measurement results during follow-up throughout days 1, 2, 3, and 7 were recorded. Partial carbon dioxide pressure (PCO_2) was numerically higher in the APRV group, although there was no statistically significant difference between the groups. Partial oxygen pressure (PO_2) did not differ between the groups; however, the P/F ratio was higher in the APRV group on all four days (p = 0.032). FiO_2 ratios were lower in the APRV group on days 2, 3 and 7, and the difference on day 7 was statistically significant (p = 0.011) (Fig. 2).

The P_{mean} on mechanical ventilator was significantly lower in the P-SIMV+PS group on all four days. P_{peak} was significantly lower in the P-SIMV+PS group on day 1 (p = 0.015), while no significant difference was present on the other days.

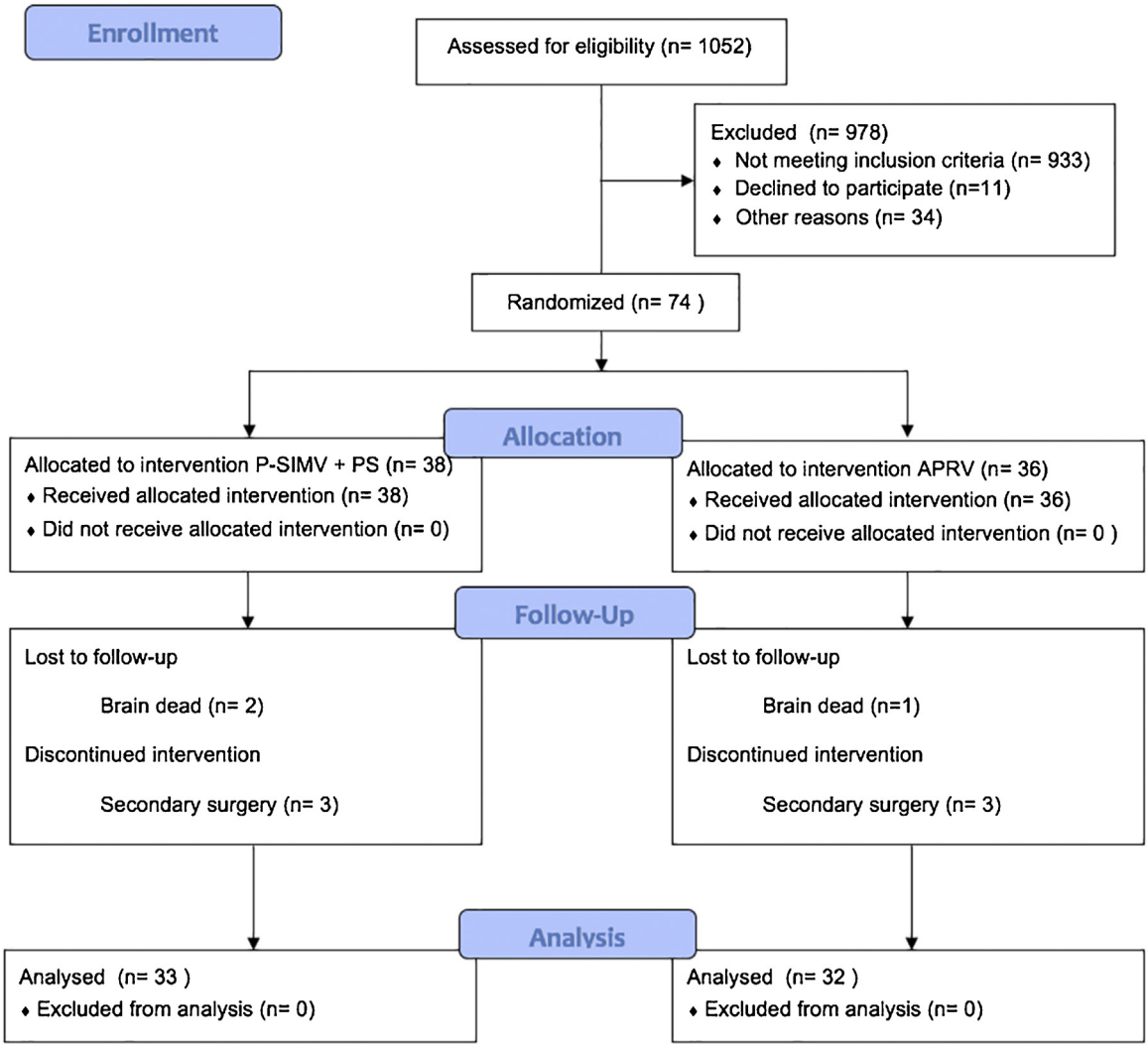

Figure 1 Flow diagram.

Table 4 Comparison of outcomes after exclusion of deceased patients.

	P-SIMV+PS	APRV	*p*
Weight (kg)[a]	83.5 (60–95)	82.5 (34–120)	0.646
LIPS[a]	9 (7–11)	8.5 (7–12)	0.443
APACHE II[a]	16 (7–24)	17 (7–35)	0.164
SOFA[a]	4.5 (3–10)	6.5 (3–17)	0.050
Sedation (total/day)[a]	6.5 (2–65)	3 (1–18)	0.170
Vasopressor/Inotrope (total/day)[a]	2 (1–15)	6.5 (1–14)	0.093
MV/Extubation duration (total/day)[a]	10 (3–65)	8 (2–26)	0.211
ICU stay (day)[a]	23.5 (10–81)	11 (2–58)	0.027
Hospital stay (day)[a]	33 (17–85)	25.5 (8–79)	0.297

LIPS, Lung injury prediction score; APACHE II, Acute Physiology, Age, Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; ARDS, Acute respiratory distress syndrome; MV, mechanical ventilation; ICU, intensive care unit.
All values are shown as med (min–max).
[a] Mann Whitney U test, $p < 0.05$.

Discussion

Our results showed improved oxygenation, increased mean airway pressure, and reduced length of ICU stay with the use of APRV compared to the P-SIMV+PS method in patients with a high risk of ARDS development as determined by LIPS score. Nevertheless, there was no difference between the two groups regarding incidence rate of ARDS development,

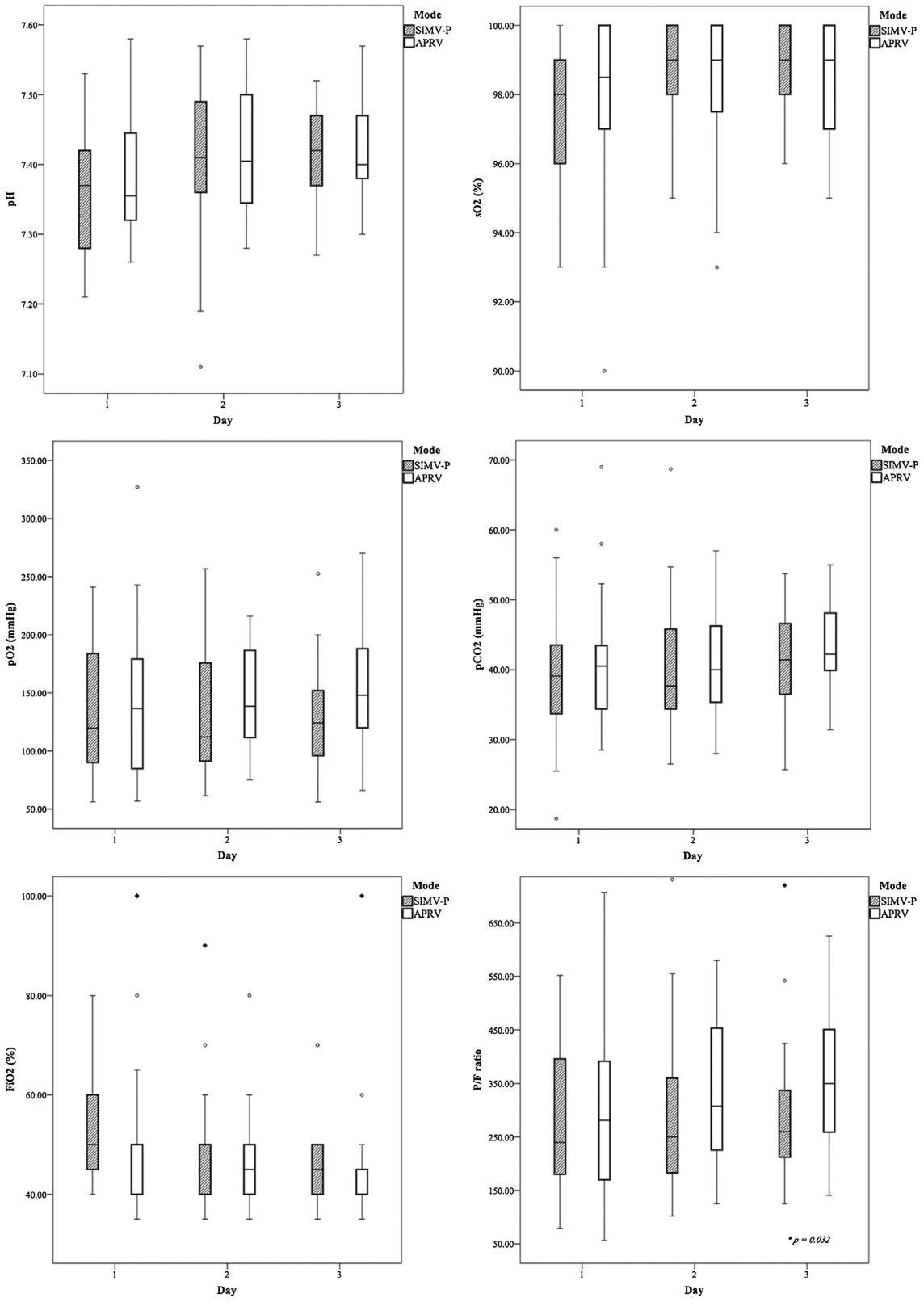

Figure 2 Box-plots graphics of arterial blood gases on follow-up days. *Footnotes*:
Each figure shows different arterial blood gas parameters in follow up for the first three days of the SIMV-P and APRV groups.
♦, o show outlier values. *shows statistically significant difference on the day between SIMV-P and APRV groups.
PCO_2, partial pressure of carbon dioxide; PO_2, partial pressure of oxygen; SO_2, arterial oxygen saturation; P/F, ratio of partial pressure of oxygen to the fraction (%) of inspired oxygen; and FiO_2, the fraction (%) of inspired oxygen.

which was the primary outcome of the study. There are several studies in literature showing improved oxygenation with early use of APRV mode in patients with ARDS.[4–8]

LIPS is a scoring system that recognizes patients with high risk of ARDS at the early period as soon as they are admitted to the ICU.[16] Bauman Z.M. et al showed that a LIPS score above 7 was significantly associated with the risk of ARDS development.[10] This score was initially evaluated on surgical patients, and was validated for a wide range of patient types including trauma patients. While surgical patients and potentially trauma patients were of primary concern of this score, it was also validated in a group of patients under the risk of shock, sepsis, and/or multiple organ dysfunction.[17,18]

ARDS occurred in a total of 6 out of 65 patients in the entire study group; only one of them was in the APRV group. This result suggests that, despite being able to prognosticate patients with more serious disease, LIPS score was not quite successful in predicting ARDS. This finding may be due to our heterogeneous and limited patient population. While the number of patients developing ARDS was less in the APRV group (3.1%), the difference was statistically insignificant.

There are several human and animal studies in literature that have compared APRV against the conventional modes.[19–22] Most of these studies are observational studies with a limited number of patients. While these have found improved oxygenation with the application of APRV mode, mortality has been evaluated in only a few studies; no difference has been found regarding mortality in comparison to other modes[3,8] On the other hand, Carsetti et al detected reduction in hospital mortality as well in a recent study including acute hypoxemic patients.[23]

We found significantly improved oxygenation in the APRV group. The PaO_2/FiO_2 ratios, in particular, were numerically higher on all four days of follow-up in the APRV group. This difference became significant on day 3. The FiO_2 ratio was lower on all days in the APRV group, and the difference was significant on day 7. Recently, Zhou et al published a study underscoring the superiorities of APRV mode.[15] In that single-centered study, the authors showed improved oxygenation and respiratory system compliance, decreased $P_{plateau}$ as well as reduced durations of both mechanical ventilation and ICU stay in the APRV group. However, similar to our results, they did not find a difference in terms of mortality or hospital stay. A major limitation of that study by Zhou et al was reported as a lack of homogeneity between the groups with a greater number of comorbid conditions in the control group. Compared to our results, Zhou and colleagues results are quite different and the reason for these differences needs to be further investigated. Similar to our results, however, Maxvel et al did not find a reduced sedation requirement.[22]

In contrast to many other studies, they found an increase in ventilator days, ICU length of stay, and ventilator-associated pneumonia. They attributed these results to high baseline APACHE II (Acute Physiology and Chronic Health Evaluation II) scores of the patients.[22] These contradicting results can certainly be explained by the difference in patient populations. A distinction of our study, on the other hand, is that we documented favorable results when APRV mode is applied as a preemptive treatment to non-ARDS patients with healthy lung tissue.

One of these favorable effects was that mean airway pressure on mechanical ventilator was higher in APRV group on all four days of follow-up. Due to the inverse I/E ratio, APRV results in higher P_{mean} than conventional lung-protective ventilation. In APRV, T_{high} is way longer than T_{low}; and therefore, it yields a higher P_{mean} for the same P_{peak} compared to the conventional ventilation. Time spent at high pressure in APRV generally corresponds to 80–90% of the respiratory cycle. A higher P_{mean} is directly proportional to PaO_2 due to alveolar recruitment. For all these reasons, high P_{mean} has been shown to be beneficial in ARDS patients (due to surfactant deactivation, atelectasis, and alveolar edema).[24,25] J-Q Li et al also compared the SIMV and APRV groups and found higher P_{mean} values in the APRV group, which is similar to our results.[26] Contrary to our work, they included moderate and severe ARDS patients in the APRV group and found P_{mean} on day one as 21.2 ± 5.3 cm H_2O. In our study, P_{mean} was lower [16 (15–18.75) cmH_2O] compared to what was reported by J-Q Li et al (2016), although we found this value to be higher in the APRV group than in the conventional mode. This result shows that APRV mode can be used as a lung-protective method with increased patient comfort even with lower pressures in patients with spontaneous breathing who do not have ARDS. The fact that we did not observe complications, such as pneumothorax or arrhythmia, in our study patients may also be attributed to this lower airway pressures. Another interesting point is that patients did not develop hypercapnia even with low pressures and long T_{high} times. This can be explained by preservation of spontaneous respiration, improved V/Q ratio, and opening of microatelectasis (if present).[3]

In our study, the length of ICU stay was significantly shorter in the APRV group. The mechanical ventilation time was also shorter in the APRV group with a median of 7.5 days; however, the difference was statistically not significant. Similarly, there have been other studies reporting shorter ICU stay with APRV application.[5,27] Possible reasons for this may be improvements in pulmonary functions such as gas exchange and respiratory compliance and a reduced need for sedation and paralysis with early use of APRV mode.[27–29] We did not find significant reduction in total sedation requirement; however, we did not evaluate the administered cumulative dose.

There are several limitations to this study. We did not evaluate patient ventilator asynchrony or the effect of the ability to respire spontaneously on patient compliance. Additionally, we did not evaluate the effects of APRV and conventional modes on patient mechanics. Another limitation was the limited number of patients due to an abundance of exclusion criteria. In addition, the surgical patient population was higher, which was thought to result in detection of less ARDS development than predicted with the LIPS score. For that reason, the ARDS-protective effect of APRV, which was the primary outcome, could not be evaluated effectively. Lastly, we did not evaluate total sedation dose although we examined whether patients had sedation requirement.

In conclusion, APRV can safely be used preemptively in selected groups of surgical and medical patients with preserved spontaneous breath in order to make benefit of its lung-protective effects. However, it does not reduce ARDS development or mortality. In comparison to the conventional

mode, it is associated with improved oxygenation, higher mean airway pressures, and shorter ICU stay length. This study is one of the few studies including the patients with a high risk of ARDS that do not require high PEEP levels; nevertheless, it should be confirmed with larger scale studies.

Conflicts of interest

The authors declare no conflicts of interest.

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