



# Changes of blood gas analysis in moderate-to-severe acute respiratory distress syndrome patients during long-term prone position ventilation: a retrospective cohort study

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**Background:** Prone position ventilation (PPV) has been recommended for patients with acute respiratory distress syndrome (ARDS) to improve oxygenation. However, whether prolonged prone ventilation will aggravate hyperoxia and whether abdominal compression will aggravate permissive hypercapnia acidosis are topics of concern. We carried out a retrospective analysis to investigate the issues above.

**Methods:** Clinical data were collected from 97 moderate-to-severe ARDS patients who received PPV as part of their treatment in the intensive care unit (ICU) of the First Affiliated Hospital of Guangzhou Medical University from November 2015 to May 2021. We collected arterial blood gas of patients according to the 3 periods: supine position ventilation (SPV), PPV early stage (within 4 hours), and PPV middle and late stage (6 hours or later). We established a linear mixed-effects models with “body position changes, times of PPV, gender, age, baseline SOFA, and baseline APACHE II” as fixed effects, and individual and the number of prone positions as random intercept and random slope to investigate the effect of body position changes on blood gas analysis.

**Results:** Among the 97 patients received PPV included, 51 were ICU survivors. Arterial partial pressure of oxygen (PaO<sub>2</sub>) and PaO<sub>2</sub>/fraction of inspired oxygen (FiO<sub>2</sub>) ratio were significantly higher at the early, middle and late stages of PPV than those in SPV [PFR (mmHg): 158 (118.00, 203.00) vs. 161 (129.00, 202.75) vs. 123 (91.75, 163.00), P<0.05]. Despite the synchronized reduction of FiO<sub>2</sub>, the incidence of hyperoxia in the prone position was still significantly higher than that in the supine position [hyperoxia (%): 33.33 vs. 33.56 vs. 12.42, P<0.05]; there was no significant change in arterial carbon dioxide partial pressure (PaCO<sub>2</sub>) at each stage of PPV, but there was a significant increase in PH at PPV middle and late stages than those at early stage [PH: 7.39 (7.34, 7.42) vs. 7.37 (7.31, 7.41), P<0.05].

**Conclusions:** Although PPV improves the patients' oxygenation, the associated incidence of hyperoxia exceeds 33%. Down-regulate FiO<sub>2</sub> more sharply after PPV is necessary, if oxygenation conditions permit. PPV may alleviate the acidosis associated with permissive hypercapnia in ARDS patients treated with lung protective ventilation strategy (LPVS).

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## Introduction

Prone position ventilation (PPV), which has been shown to be able to improve the prognosis of acute respiratory distress syndrome (ARDS) patients (1), has good social and economic benefits (2). The ARDS prone position network (APRONET) cross-sectional survey conducted in 2017 showed that the utilization rate of PPV in ARDS patients had already reached 32.9% (3). PPV helps to increase the arterial partial pressure of oxygen (PaO<sub>2</sub>) in most ARDS patients (by up to 70%) (4-6). Furthermore, oxygenation tends to be improved within the first hour in most cases (7). Even for pulmonary ARDS, the improvement in oxygenation reaches a steady state in about 3 hours. Lee *et al.*'s research findings (8) suggest that oxygenation was improved by over 53% in patients during the first application of PPV, and that oxygenation would continue to be improved for several hours after the implementation

of supine position ventilation (SPV). When PPV was repeated, oxygenation would be further improved. Regarding the concept of lung protective ventilation (LPV), the PROSEVA study (1) suggests conducting PPV when PaO<sub>2</sub>/fraction of inspired oxygen (FiO<sub>2</sub>) ratio (PFR) is lower than 150 mmHg. For patients with a good response, a concern is whether the incidence of hyperoxia may increase, making it worthwhile to retrospectively analyze the rule of improvement in oxygenation during long-term PPV. The prone position is an unconventional body position. With increasing elastic resistance in the chest and abdomen in the prone position, whether it is necessary to urgently adjust the tidal volume and respiratory rate or not is unclear. Owing to the impact of hypercapnia on all visceral organs, PPV may match ventilation/blood perfusion and improve the right heart function later than the improvement of oxygenation—thus, the effect of early PPV on carbon dioxide partial pressure (PaCO<sub>2</sub>) is poorly understood. Given low tidal volume LPVS, it is worthwhile to evaluate the effect of prolonged PPV on permissive hypercapnia (9,10); at present, there is no study on the dynamic changes of hyperoxia and permissive hypercapnia during prolonged PPV. In this study, all blood gas indexes were collected before and after each application of PPV in patients to investigate their dynamic change rule in order to offer better guidance on clinical adjustment. We present the following article in accordance with the STROBE reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-5907/rc>).

### Highlight box

#### Key findings

- Prone position ventilation (PPV) improves the patients' oxygenation, however, the associated incidence of hyperoxia exceeds 33%. PPV may alleviate the acidosis associated with permissive hypercapnia in acute respiratory distress syndrome (ARDS) patients treated with lung protective ventilation strategy (LPVS).

#### What is known and what is new?

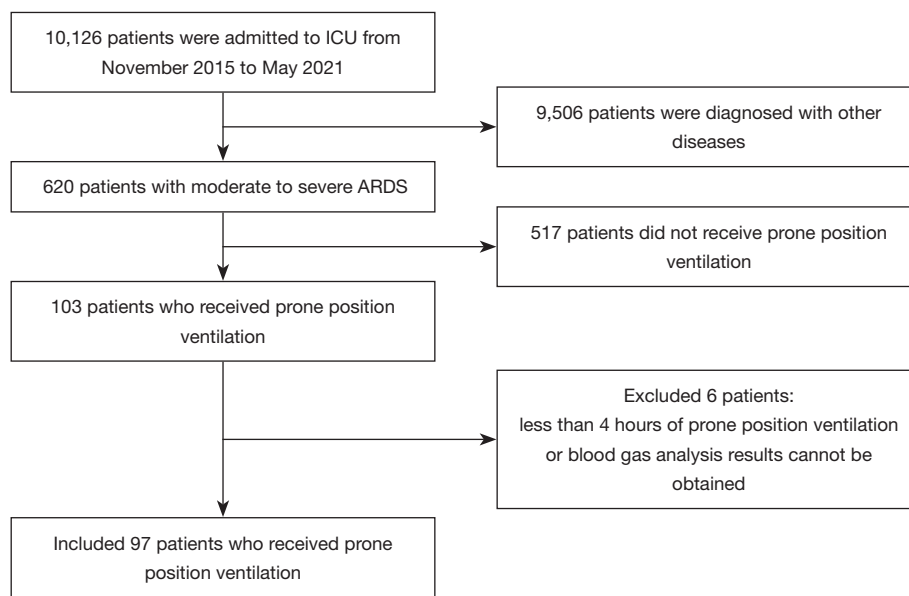
- PPV is widely used to improve the oxygenation and prognosis of patients with moderate-to-severe ARDS.
- We report that the incidence of hyperoxia after PPV is as high as 33%, which deserves attention. With increasing elastic resistance in the chest and abdomen in the prone position, the acidosis associated with permissive hypercapnia do not aggravate.

#### What is the implication, and what should change now?

- On the premise of ensuring tissue oxygenation, it is necessary to down-regulate FiO<sub>2</sub> more sharply in accordance with patients' conditions after PPV. Prolonged PPV can improve oxygenation in moderate-to-severe ARDS patients without exacerbating permissive hypercapnia caused by LPVS.

## Methods

This was a retrospective observational cohort study of adult patients (≥18 years) with ARDS. The inclusion criteria were as follows: (I) adult patients (age ≥18 years) who accepted treatment in the intensive care unit (ICU) of the First Affiliated Hospital of Guangzhou Medical University from November 2015 to May 2021; (II) patients who were diagnosed with ARDS according to the Berlin definition; (III) during hospitalization, underwent PPV



**Figure 1** Flowchart of the study. ICU, intensive care unit; ARDS, acute respiratory distress syndrome.

at least once. The exclusion criteria were as follows: (I) inability to tolerate the PPV treatment and the duration of PPV was less than 4 hours; (II) patients did not undergo blood analysis during PPV or the blood gas analysis results could not be traced. During the study period, 10,126 patients were admitted to our ICU ward, 620 patients with moderate to severe ARDS were diagnosed, and 103 of these patients received PPV. A total of 6 patients who received PPV for less than 4 hours or whose blood gas analysis results were unable to be obtained were excluded from the study. A total of 97 patients receiving PPV were included in this study (*Figure 1*). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (Document No. 34 [2017]). Individual consent for this retrospective analysis was waived. The chief clinician decided whether to continue or stop PPV. PPV was terminated immediately if any patient experienced unstable hemodynamics, arrhythmia, tracheal displacement, or other types of life-threatening deterioration during the treatment. In our study, most of patients involved received PPV for 12–16 hours in total each day, and PPV was performed at an interval of 8 hours.

A total of 885 blood gas analyses were collected from the 97 patients included, which were grouped into SPV, PPV early stage (within 4 hours), and PPV middle and late

stage (4–16 hours) according to patients' body positions and duration of PPV when blood gas analysis was conducted (*Figure S1*).

#### Data collection

The following general information of patients was collected: gender, age, date of admission, date of transfer to ICU, acute physiological and chronic health evaluation II (APACHE II), sequential organ failure assessment (SOFA), Richmond Agitation-Sedation Scale (RASS), whether neuromuscular blockade was applied or not, principal diagnosis, outcome, and so on. The results of blood gas analysis including PH, PaCO<sub>2</sub>, PaO<sub>2</sub>, FiO<sub>2</sub>, and PFR were collected before (SPV) and after (PPV) each body position change, including PPV early stage and PPV middle and late stage.

#### Statistical methods

Linear mixed-effects models, taken from LmerTest (v. 3.1-3) and lme4 (v. 1.1.27-1) in R language (v. 4.1.2; The R Foundation of Statistical Computing, Vienna, Austria), were used to test the effect of body position changes on the blood gas indexes. Then, Satterthwaite's method was used to generate P values for the mixed models. This method can be used to explore multiple factors and

**Table 1** Characteristics of the patients at baseline

Baseline data	Value
Age (years), mean $\pm$ SD	56.52 $\pm$ 14.13
Male, n (%)	68 (70.10)
Neuromuscular blockade, n (%)	48 (49.48)
APACHE II, mean $\pm$ SD	20.14 $\pm$ 6.88
RASS, median (1st–3rd quartile)	–4 (–4, –4)
Pre-prone blood gases, median (1st–3rd quartile)	
PH	7.37 (7.30, 7.41)
PaCO <sub>2</sub> (mmHg)	50.10 (43.85, 60)
PaO <sub>2</sub> (mmHg)	81.90 (68.55, 103.50)
FiO <sub>2</sub>	0.80 (0.63, 1.00)
PaO <sub>2</sub> /FiO <sub>2</sub> (mmHg)	102.35 (81.05, 146.25)
Principal diagnosis, n [%]	
Septic shock	11 [11]
CTD	26 [27]
Pulmonary infection	33 [34]
Postoperative patient	12 [12]
Blood disease	9 [9]
COPD	4 [4]
Barotrauma	2 [2]
ICU outcome, survival	51 [53]

SD, standard deviation; APACHE, acute physiological and chronic health evaluation; RASS, Richmond Agitation-Sedation Scale; CTD, connective tissue disease; ICU, intensive care unit.

covariates simultaneously with the variance among cases taken into consideration. The models were initially fitted with a random intercept and random slope taken for every case. Model comparisons were made using the maximum likelihood (ML) method to compare the models under different stochastic effects, which were finally trimmed into those containing significantly improved model fitting performance only. After random-effects models were determined, the same method was applied to the selection of fixed effects. The function was used to identify or rule out a singular fit. We finally selected “body position changes, times of PPV, gender, age, baseline SOFA, and baseline APACHE II” as fixed effects for optimal mixed-effects models. There was a random intercept and random slope for individuals when they were affected by the number of prone positions. Blood gas analysis indicators such as

“PH, PaCO<sub>2</sub>, PaO<sub>2</sub>, FiO<sub>2</sub>, PFR” are dependent variables. The enumeration data were checked using the chi-squared test. Further, unless otherwise stated, a 2-tailed P value of <0.05 was considered statistically significant.

## Results

### Baseline data

Among the 97 patients, 68 were male while 29 were female; the average age was (56.52 $\pm$ 14.13); 11 cases were diagnosed with septic shock, 26 were diagnosed with connective tissue disease (CTD), 33 were diagnosed with pulmonary infection, 12 were postoperative patients, 9 were diagnosed with the hematologic disease, 4 with chronic obstructed pulmonary disease (COPD), and 2 with barotrauma. The overall survival rate of patients was 53% (Table 1).

### Incidence rate of hyperoxia

Compared with SPV, PPV early stage and PPV middle and late stage saw higher incidence of hyperoxia (P<0.05) (Table 2, Figure 2).

### Blood gas analysis changes before and after PPV

PH was significantly higher at PPV middle and late stage than in SPV (P<0.05); there was no significant difference in PaCO<sub>2</sub> among SPV, PPV early stage, and PPV middle and late stage (P>0.05); compared with SPV, PaO<sub>2</sub> was significantly higher at PPV early stage and PPV middle and late stage, and the difference was statistically significant (P<0.05); compared SPV, FiO<sub>2</sub> was significantly lower at PPV early stage and PPV middle and late stage, and it further decreased at PPV middle and late stage compared to PPV early stage (P<0.05); PaO<sub>2</sub>/FiO<sub>2</sub> was significantly higher at PPV early stage and PPV middle and late stage than SPV, and the difference was statistically significant (P<0.05) (Table 3, Figure 3).

### Multivariate analysis and blood gas indexes

PH and PaO<sub>2</sub>/FiO<sub>2</sub> were positively correlated with times of PPV and negatively correlated with FiO<sub>2</sub>, namely, with the passage of time, PH and PaO<sub>2</sub>/FiO<sub>2</sub> showed an increasing trend whereas FiO<sub>2</sub> showed a decreasing trend (P<0.05); FiO<sub>2</sub> was positively correlated with the baseline SOFA score and negatively correlated with PH, namely, the higher the

**Table 2** Proportion of patients with hyperoxia before and after PPV

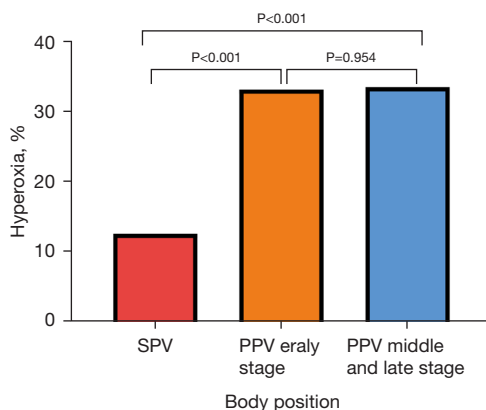
	Stage		
	SPV [1]	PPV early stage [2]	PPV middle and late stage [3]
Hyperoxia	39 (12.42%)	93 (33.33%)	98 (33.56%)
Non-hyperoxia	275 (87.58%)	186 (66.67%)	194 (66.44%)
Total	314	279	292

P value: 1 vs. 2,  $P < 0.001$ ; 1 vs. 3,  $P < 0.001$ ; 2 vs. 3,  $P = 0.954$ . PPV, prone position ventilation; SPV, supine position ventilation.

**Table 3** Effects of PPV on blood gas (n=97)

Blood gases	Stage			P value
	SPV	PPV early stage	PPV middle and late stage	
PH	7.38 [7.32, 7.41]	7.37 [7.31, 7.41]	7.39 [7.34, 7.42] <sup>b</sup>	<0.05
PaCO <sub>2</sub>	51.00 [45.35, 59.13]	51.50 [45.30, 61.00]	50.20 [44.30, 58.80]	>0.05
PaO <sub>2</sub>	84.65 [70.85, 104.85]	103.00 [86.10, 128.00] <sup>a</sup>	108.10 [88.53, 128.00] <sup>a</sup>	<0.05
FiO <sub>2</sub>	0.70 [0.60, 0.85]	0.70 [0.57, 0.80] <sup>a</sup>	0.66 [0.60, 0.80] <sup>a,b</sup>	<0.05
PFR	123.00 [91.75, 163.00]	158.00 [118.00, 203.00] <sup>a</sup>	161.00 [129.00, 202.75] <sup>a</sup>	<0.05

Data are expressed as median [interquartile range]. <sup>a</sup>,  $P < 0.05$  vs. SPV; <sup>b</sup>,  $P < 0.05$  vs. early PPV. PPV, prone position ventilation; SPV, supine position ventilation; PaCO<sub>2</sub>, carbon dioxide partial pressure; PaO<sub>2</sub>, partial pressure of oxygen; FiO<sub>2</sub>, fraction of inspired oxygen; PFR, PaO<sub>2</sub>/FiO<sub>2</sub>.

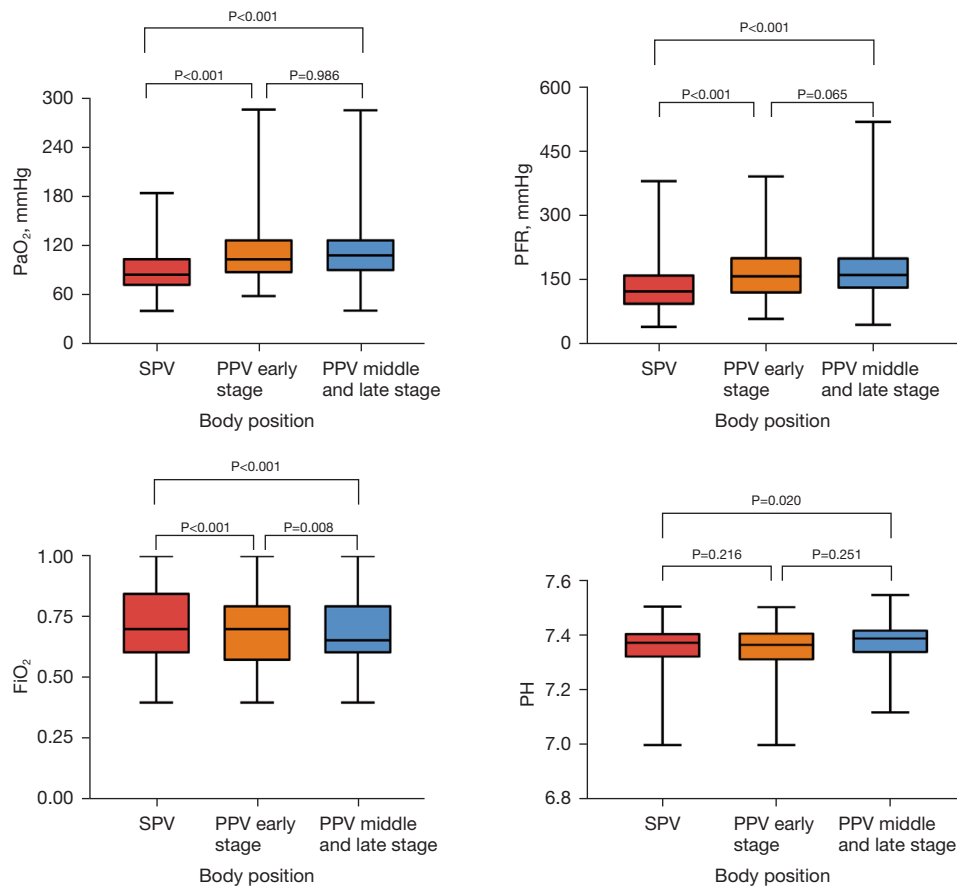
**Figure 2** Proportion of patients with hyperoxia with body position. SPV, supine position ventilation; PPV, prone position ventilation.

baseline SOFA score, the higher FiO<sub>2</sub>, and the lower PH ( $P < 0.05$ ); blood gas indexes were not significantly correlated with gender, age, and baseline APACHE II (Table 4).

## Discussion

Compared with SPV, there was an average rise of 35 and

38 mmHg in patients' PFR at PPV early and middle-and-late stage, suggesting the continuous improvement of oxygenation in long-term PPV, which was consistent with the results of a previous study (1). The incidence of hyperoxia in the ICU could reach 50% according to previous studies, which was closely related to the length of stay and mortality rate (11,12), but clinicians pay far less attention to hyperoxia than to hypoxia, especially when FiO<sub>2</sub> has dropped below 60% (13). In this study, PaO<sub>2</sub> rose after the patients underwent PPV, with the median PaO<sub>2</sub> fluctuating from 84.65 to 108.10 mmHg. Some 33.3% of the patients were diagnosed with hyperoxia (PaO<sub>2</sub>  $\geq 120$  mmHg) (14) at the PPV early stage, whereas 33.6% were diagnosed with hyperoxia at PPV middle and late stage, both significantly higher than those at SPV; hyperoxia makes it possible to generate reactive oxygen species (ROS) and free radicals, which have pro-inflammatory and cytotoxic effects, causing oxidative stress and neuron injuries, which may aggravate the damage to multiple organs including the heart, lung, kidney, and brain (15-17). A recent observational study indicated a U-shaped relationship between PaO<sub>2</sub> and mortality in ARDS patients, with a minimum mortality risk when PaO<sub>2</sub>



**Figure 3** Changes of blood gas with body position. PaO<sub>2</sub>, partial pressure of oxygen; SPV, supine position ventilation; PPV, prone position ventilation; PFR, PaO<sub>2</sub>/FiO<sub>2</sub>; FiO<sub>2</sub>, fraction of inspired oxygen.

**Table 4** Effects of multivariate analysis on blood gas (n=97)

Blood gases	Times	Baseline SOFA	Sex, male	Age	Baseline APACHE II
PH	0.011 <sup>c</sup>	0.003 <sup>d</sup>	>0.05	>0.05	>0.05
PaCO <sub>2</sub>	>0.05	>0.05	>0.05	>0.05	>0.05
PaO <sub>2</sub>	>0.05	>0.05	>0.05	>0.05	>0.05
FiO <sub>2</sub>	<0.001 <sup>d</sup>	0.003 <sup>c</sup>	>0.05	>0.05	>0.05
PFR	0.007 <sup>c</sup>	>0.05	>0.05	>0.05	>0.05

<sup>c</sup>, estimate >0; <sup>d</sup>, estimate <0. Time represents the frequency of PPV. SOFA, sequential organ failure assessment; APACHE, acute physiological and chronic health evaluation; PaCO<sub>2</sub>, carbon dioxide partial pressure; PaO<sub>2</sub>, partial pressure of oxygen; FiO<sub>2</sub>, fraction of inspired oxygen; PFR, PaO<sub>2</sub>/FiO<sub>2</sub>; PPV, prone position ventilation.

was at 93.8–105 mmHg (18); moreover, at PPV early stage and PPV middle and late stage in this study, the chief physician took the initiative to down-regulate FiO<sub>2</sub> with the improvement of oxygenation, but the median remained above 0.7. Hyperoxia can directly damage bronchial alveolar

epithelium, aggravating mechanical ventilation-related lung injuries (19,20), increasing the risk of oxygen poisoning and ventilator-associated pneumonia (VAP) (21). Especially at PPV middle and late stage, median FiO<sub>2</sub> further decreased to 0.66, but there was still a slow increase in the proportion

of patients with hyperoxia.

There is a long controversy over the research on liberal oxygen therapy and conservative oxygen therapy. ARDS patients mostly experience hypoxemia-related complications at the early stage. Although a clear recommendation on PaO<sub>2</sub> from ARDSnet (22), clinicians, who are still concerned about histanoxia, risk taking hyperoxia as a means of raising oxygen reserves (23), but actually, there are many factors affecting oxygen delivery. Despite the lack of evidence for a significant dose-effect relationship between PaO<sub>2</sub> and mortality, the number of days with PaO<sub>2</sub> >120 mmHg is an independent risk factor for VAP (17). The HYPER2S randomized controlled trial (RCT) suggests that patients with hyperoxia experience more severe ICU-acquired weakness, and the mortality increases on day 28 after complication with lactic acid elevation (24,25). Most of the cases included in this study were pulmonary ARDS patients with septic shock. The data suggested that FiO<sub>2</sub> was positively correlated with the baseline SOFA score and negatively correlated with PH. In other words, the higher the baseline SOFA score, the higher FiO<sub>2</sub> and the lower PH. This might be related to the difference in SpO<sub>2</sub> and SaO<sub>2</sub> in response to peripheral tissue perfusion during septic shock (26). Clinicians often use higher FiO<sub>2</sub> to avoid histanoxia (13), whereas the target of oxygen therapy is relatively free. After primary diseases gradually came under control, the proportion of hyperoxia caused by PPV reached 33.6%.

Low tidal volume LPVS is normally adopted for moderate-to-severe ARDS patients, with a sedative and analgesic or even neuromuscular blocking agents used in combination to reduce abnormal central respiratory drive (27). The results of this study suggest that the median PaCO<sub>2</sub> in the patients was 50.1 mmHg before PPV, reaching the standard of permissive hypercapnia. During PPV, the anterior chest wall and abdomen were restricted, with elastic resistance increasing and minute volume decreasing. PaCO<sub>2</sub> inevitably rose further when lung homogeneity had not yet been optimally achieved after a change in the body position (9). Severe hypercapnia or a rapid rise in PaCO<sub>2</sub> could cause myocardial depression, leading to an increase in pulmonary vascular resistance (PVR), aggravating right heart insufficiency, thereby increasing the risk of inpatient death in patients with cerebral injury (28), and exacerbating concomitant symptoms such as renal injury, pulmonary injury, and so on (29,30). Is there a need to adjust the tidal volume and respiratory rate as early as possible? This study indicated

that PaCO<sub>2</sub> rose slightly at PPV early stage, but there was no significant difference from SPV, and PaCO<sub>2</sub> even decreased gradually at PPV middle and late stage; at the same time, PH showed a downward trend at PPV early stage compared with SPV, but there was no significant difference. PH tended to rise significantly at the middle-and-late stage compared with PPV early stage. A previous study revealed that the PaCO<sub>2</sub> responders had a better prognosis after PPV (31). For patients with pulmonary ARDS included in this study, a long-term prone position helped to promote systemic venous return and reduce PVR while improving oxygenation and enhancing pulmonary reexpansion, leading to an increase in cardiac output (32), thereby improving ventilation/blood flow ratio, and finally relieving acidosis.

## Conclusions

This study holds that on the premise of ensuring tissue oxygenation, it is necessary to down-regulate FiO<sub>2</sub> more sharply in accordance with patients' conditions after PPV, and select a recommended target of oxygen therapy (33) to decrease FiO<sub>2</sub> to or below 60%, so as to reduce the incidence of hyperoxia and its impact on the lung and other organs for better efficacy of PPV; prolonged PPV can improve oxygenation in moderate-to-severe ARDS patients without exacerbating permissive hypercapnia caused by LPVS.

## Limitations

There are still some shortcomings in this study, as follows: In the single-center retrospective study, blood gas indexes were primarily analyzed without any reference to oxygen toxicity-related biological indicators and cytokines; efficacy comparisons were not performed for patients with ARDS caused by different etiological factors; the outcome of patients was not taken into account, and so on.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-5907/rc>

*Data Sharing Statement:* Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-5907/dss>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-5907/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (Document No. 34 [2017]). Individual consent for this retrospective analysis was waived.

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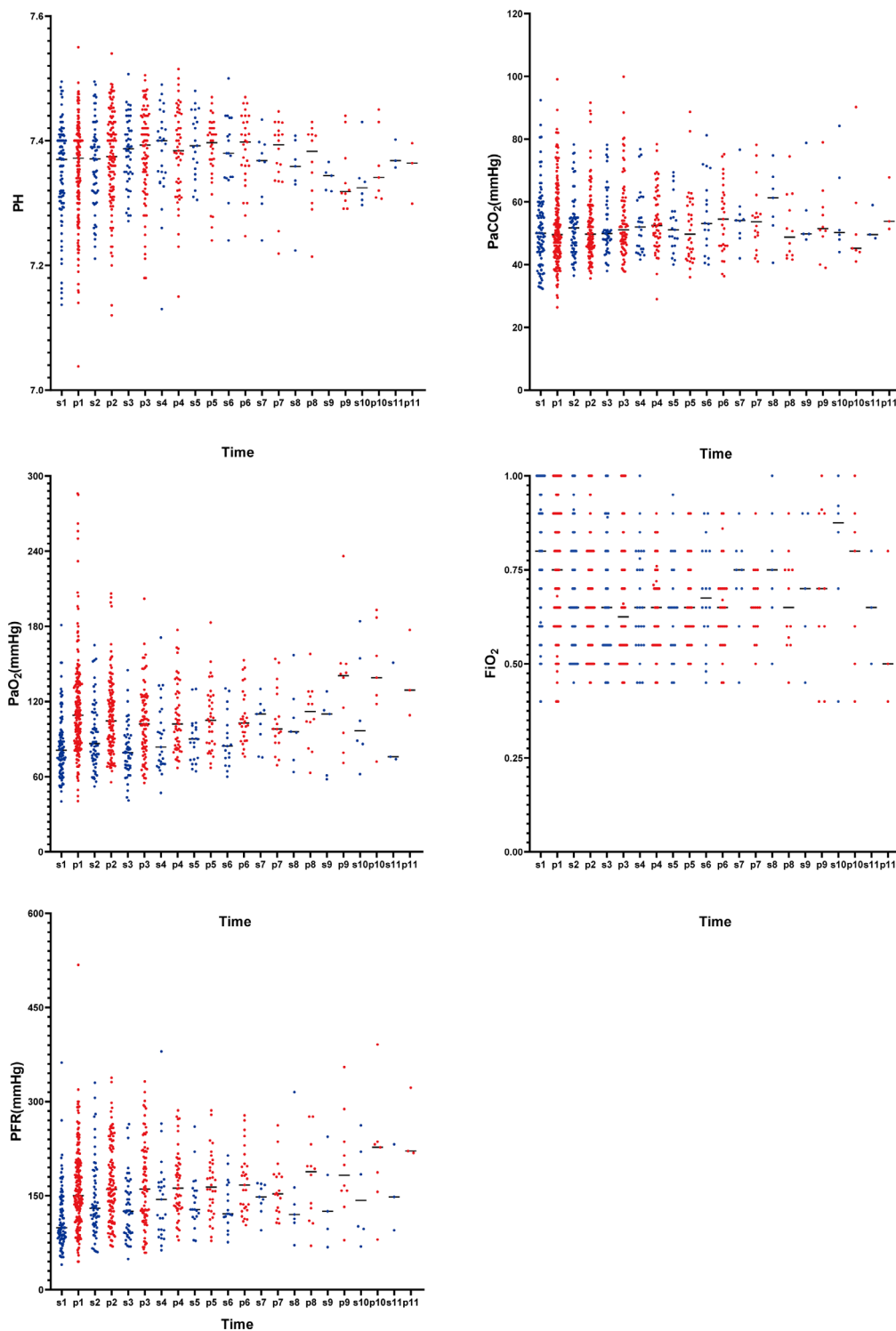
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**Figure S1** The scatter plots of the blood gas indicators of the two groups (SPV *vs.* PPV) for different time-points. The figure shows the blood gas of all patients with 11 times of body position changes. Since only one patient had more than 12 times of prone ventilation, the blood gas was not displayed after 12 times. The unit of measurement time is the number of changes in prone position. SPV, supine position ventilation; PPV, prone position ventilation; PaCO<sub>2</sub>, carbon dioxide partial pressure; PaO<sub>2</sub>, partial pressure of oxygen; FiO<sub>2</sub>, fraction of inspired oxygen; PFR, PaO<sub>2</sub>/FiO<sub>2</sub>; s1, the first time of supine position ventilation; p1, the first time of prone position ventilation.