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Effects of Different Tidal Volume Ventilation on Paraquat-Induced Acute Lung Injury in Piglets

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDE 1,2 Chao Lan
BCDEF 1,3 Jinzhu Wang
ADE 1,3 Li Li
BCF 1,2 Haina Li
CF 1,2 Lu Li
CF 1,3 Qianqian Su
CG 1,3 Lu Che
CF 1,4 Lanping Liu
CG 1,5 Min Di

1 Key-Disciplines Laboratory Clinical-Medicine Henan, Zhengzhou, Henan, China
2 Department of Emergency Intensive Care Unit, First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China
3 Department of Emergency Medicine, First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henna, China
4 Department of Anesthesiology, First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China
5 Department of Ultrasonography, First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, China

Corresponding Author: Li Li, e-mail: lilihenan@126.com
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Background: The aim of this study was to explore the effects of different tidal volume (V_T) ventilation on paraquat-induced acute lung injury or acute respiratory distress syndrome (ALI/ARDS) in piglets.

Material/Methods: We developed ALI/ARDS models in piglets by intraperitoneal injection of paraquat (PQ). The piglets were randomly divided into three groups: small V_T group (V_T=6 ml/kg, n=6), middle V_T group (V_T=10 ml/kg, n=6), and large V_T group (V_T=15 ml/kg, n=6), with the positive end-expiratory pressure (PEEP) set as 10 cmH_2O. The hemodynamics were monitored by pulse-indicated continuous cardiac output (PiCCO) and the airway pressure changes and blood gas analysis indexes were recorded at different time points. The pathological changes were observed by lung puncture.

Results: The piglets showed ALI/ARDS in 4.5±0.8 hours after PQ intraperitoneal injection. PH, PaO_2 and oxygenation indexes in the three groups all decreased after modeling success compared with baseline, and $PaCO_2$ increased significantly. PH in the small VT group decreased most obviously after ventilation for 6 hours. PaO_2 and oxygenation indexes in the small VT group showed the most obvious increase after ventilation for 2 hours and were much higher than the other two groups after ventilation for 6 hours. $PaCO_2$ increased gradually after mechanical ventilation and the small VT group showed most obvious increase. The ELWI increased obviously after ventilation for 2 hours and then the small VT group clearly decreased. PIP and plateau pressure (Pplat) in the small VT group decreased gradually and in the middle and large VT group they increased after ventilation. The lung histopathology showed that the large VT group had the most severe damage and the small VT group had only minimal damage.

Conclusions: Small tidal volume ventilation combined with PEEP could alleviate the acute lung injury induced by paraquat and improve oxygenation.

MeSH Keywords: Acute Lung Injury • Paraquat • Tidal Volume

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Background

Paraquat (PQ) poisoning results in a high rate of mortality. A research report from the Chinese Center for Disease Control and Prevention showed that the incidence of paraquat poisoning increased by about 47.35% a year on average from 2002 to 2010 [1]. The mortality of paraquat poisoning in foreign countries is about 33%–50% [1]. Although the survival rate of PQ poisoning increased with the improvement of medical levels, there were still a considerable number of patients who died after large doses of oral PQ [2]. Moderate and severe PQ poisoning was mainly characterized by acute lung injury in the early stage and pulmonary fibrosis in the advanced stage [3]. When the patients showed ALI/ARDS or progressive pulmonary fibrosis, the conventional treatment was ineffective. Lemaire et al. [4] used continuous positive airway pressure (CPAP) to treat PQ poisoning patients with respiratory failure and the patients died in 15 days. Histopathology showed overexpansion of pulmonary parenchyma, suggesting that although CPAP ventilation could increase lung volume, it might cause lung overexpansion and aggravate lung injury. Lung protective strategies of ventilation (LPVS) has been proposed to treat ALI/ARDS in recent years, which advocated small VT ventilation (6~8 ml/kg), permissive hypercapnia, and maintaining alveolus opening by using PEEP [5]. At present, treating PQ-induced acute lung injury by LPVS still lacks support from basic and clinical research. The present study was conducted to investigate the effects of different VT PEEP on PQ-induced acute lung injury, blood gas analysis indexes, oxygenation index, and hemodynamics and aimed to provide theoretical guidance for the clinical application of mechanical ventilation.

Material and Methods

Experimental animals

Eighteen female piglets (65–70 days, 25.0±2.1 kg) were obtained from the Experimental Animal Center of Henan Province, Zhengzhou, China. The piglets were provided with water ad libitum and fasted 12 hours before the operation. After intramuscular injection of atropine (0.05 mg/kg) (Harvest Pharmaceutical Co. Ltd, Shanghai, China) and ketamine (15 mg/kg) (Fujian Gutian Pharmaceutical Co. Ltd, Gutian, China), the piglets were placed supine on a table with continuous ECG monitoring and ear-vein injection of Ringer lactate solution (10 ml/kg·h). The piglets received mechanical ventilation and the settings of volume controlled ventilation (VCV) were: V_T=12 ml/kg, RR=30 breath/min, Inspiratory/Expiratory=1:2, fraction of inspired oxygen (FiO_2)=30%, PEEP=0 cmH_2O. The central venous catheter was set by jugular vein and the PICCO catheter was set by femoral artery. Each piglet received intraperitoneal injection of 20 ml 20% PQ solution (Sigma, St. Louis, MO, USA) and the arterial blood gas analysis was measured every 30 minutes until $PaO_2/FiO_2 \leq 300$ mmHg. The $PaO_2/FiO_2 \leq 300$ mmHg in 30 minutes was considered to be successfully developed the ALI/ARDS models [6]. The piglets received intravenous injection of propofol (2.5 $mg \cdot kg^{-1} \cdot h^{-1}$) (Pfizer, New York, NY, USA) and sufentanil (0.025 $\mu g \cdot kg^{-1} \cdot h^{-1}$) (Humanwell Pharmaceutical Co. Ltd., Yichang, China) throughout the process. Meanwhile, the piglets were given cis atracurium (0.1 $mg \cdot kg^{-1} \cdot h^{-1}$) (GlaxoSmithKline, London, UK) intermittently to maintain muscle relaxation. The piglets were then randomly divided into three groups: small V_T group (V_T=6 ml/kg, n=6), middle V_T group (V_T=10 ml/kg, n=6), and large V_T group (V_T=15 ml/kg, n=6), with the PEEP set as 10 cmH_2O. This study was performed in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health (Bethesda, MD, USA) Eighth Edition, 2010. The animal use protocol was reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of the First Affiliated Hospital of Zhengzhou University.

Blood gas analysis

The arterial blood was drawn at t2 (2 hours), t4 (4 hours), and t6 (6 hours) after mechanical ventilation for blood gas analysis. The recorded parameters of PH, PaO_2, $PaCO_2$, and PaO_2/FiO_2 were calculated.

PiCCO monitoring

The PiCCO temperature sensor was connected with the jugular vein catheter and the PiCCO detector was connected with the femoral artery catheter. We rapidly injected 10 ml ice saline (0–4°C) via the jugular vein catheter and recorded ELWI, PVPI, heart rate (HR), and mean arterial pressure (MAP) each time at baseline (before ALI/ARDS modeling), t0, t2, t4, and t6.

Histological studies

Tissues of the right lower lobe of the lung were fixed in 4% paraformaldehyde at room temperature, embedded in paraffin, sectioned serially at 10 μm, and stained with hematoxylin and eosin (HE).

Statistical analysis

All data were analyzed using SPSS17.0 software (SPSS Inc., Chicago, IL, USA). All data are expressed as the mean ± standard deviation. The data were analyzed by unpaired Student's t test for comparison of same group at different time and χ^2 test for comparison of different groups at same time. A p value <0.05 or p value <0.01 was considered statistically significant.

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Table 1. Comparison of HR and MAP.

Items	Groups	n	Baseline	t_0	t_2	t_4	t_6
HR (bpm)	Small V_T	6	119.8±9.4	136.5±5.5*	94.7±7.2**	99.2±7.0**	92.8±6.2**
	Middle V_T	6	123.2±11.2	142.8±12.5*	97.3±6.4**	100.5±4.9**	98.3±8.7**
	Large V_T	6	128.0±10.3	138.8±6.8*	95.8±4.7**	104.7±5.4**	95.3±7.8**
F value			0.952	0.791	0.281	1.454	0.781
P value			0.408	0.471	0.759	0.265	0.476
MAP (mmHg)	Small V_T	6	106.8±9.7	139.0±6.5*	122.8±6.7**	110.3±8.1**	92.2±4.1**
	Middle V_T	6	104.5±9.5	136.7±7.2*	118.0±6.2**	98.7±6.7**	87.5±4.0**
	Large V_T	6	101.8±3.0	135.2±6.2*	105.5±7.0**	92.8±3.8**	85.2±3.4**
F value			0.586	0.506	10.862	11.498	5.170
P value			0.569	0.613	0.001	0.001	0.020

* Compared with baseline in the same group, P<0.05; ** compared with t_0 in the same group, P<0.05.

Results

Comparison of HR and MAP

As shown in Table 1, HR and MAP in the three groups increased after modeling success (t0) compared with baseline, with significant difference (P<0.05). HR and MAP in the three groups all decreased after mechanical ventilation compared with t0, with significant difference (P<0.05). There was no significant difference in HR in the three groups at the same time, but MAP in the three groups showed significant difference at the same time.

Arterial blood gas analysis and oxygenation index comparison

The piglets showed ALI/ARDS in 4.5±0.8 hours after PQ injection. As shown in Figure 1, PH, PaO_2, and oxygenation index in the three groups all decreased after modeling success compared with baseline, and $PaCO_2$ increased significantly (P<0.05). PH in the three groups decreased gradually after mechanical ventilation (*F*=5.392, *P*=0.000) and the small VT group decreased most obviously after ventilation for 6 hours (Figure 1A).

As shown in Figure 1B and C, PaO_2 and oxygenation index in the three groups increased after ventilation for 2 hours and then decreased gradually, with significant difference in the three groups (PaO_2: F=22.732, P=0.000; oxygenation index: F=17.148, P=0.000). PaO_2 and oxygenation index in the small VT group showed the most obvious increase after ventilation for 2 hours and was much higher than the other two groups after ventilation for 6 hours. $PaCO_2$ in the three groups increased gradually after mechanical ventilation and the small VT group showed the most obvious increase (Figure 1D).

Comparison of ELWI and VPI

The ELWI and PVPI in the three groups significantly increased after ALI/ARDS compared with baseline (Table 2). The ELWI in the three groups increased obviously after ventilation for 2 hours and then the small VT group clearly decreased. There was no significant difference in PVPI after ventilation.

Comparison of airway pressure

PIP and Pplat in the three groups increased after modeling success compared with baseline without significant difference (Figure 2). PIP and Pplat in the small VT group decreased gradually, and in the middle VT group and large VT group they increased after ventilation (PIP: *F*=13.787, *P*=0.000; Pplat: *F*=10.469, *P*=0.000). PIP and Pplat in the small VT group were much lower than in the other two groups after ventilation for 6 hours.

Comparison of lung histopathology

The alveolar walls in normal lung tissues were thin and integral and there was no abnormal exudate in the pulmonary interstitium. In ALI/ARDS models, the alveolar tissues showed obvious congestion and edema, swelling of capillary vessels, widened alveolar septum, formation of partially visible membrane, and extravasation of red blood cells in the pulmonary interstitium. After ventilation for 6 hours, the piglets in the three groups showed lung tissue fusion, further widened alveolar septum, further swelling of capillary vessels, and partial alveolar septum fracture. As shown in Figure 3, the large VT group had the most severe damage while the small VT group had only minimal damage.

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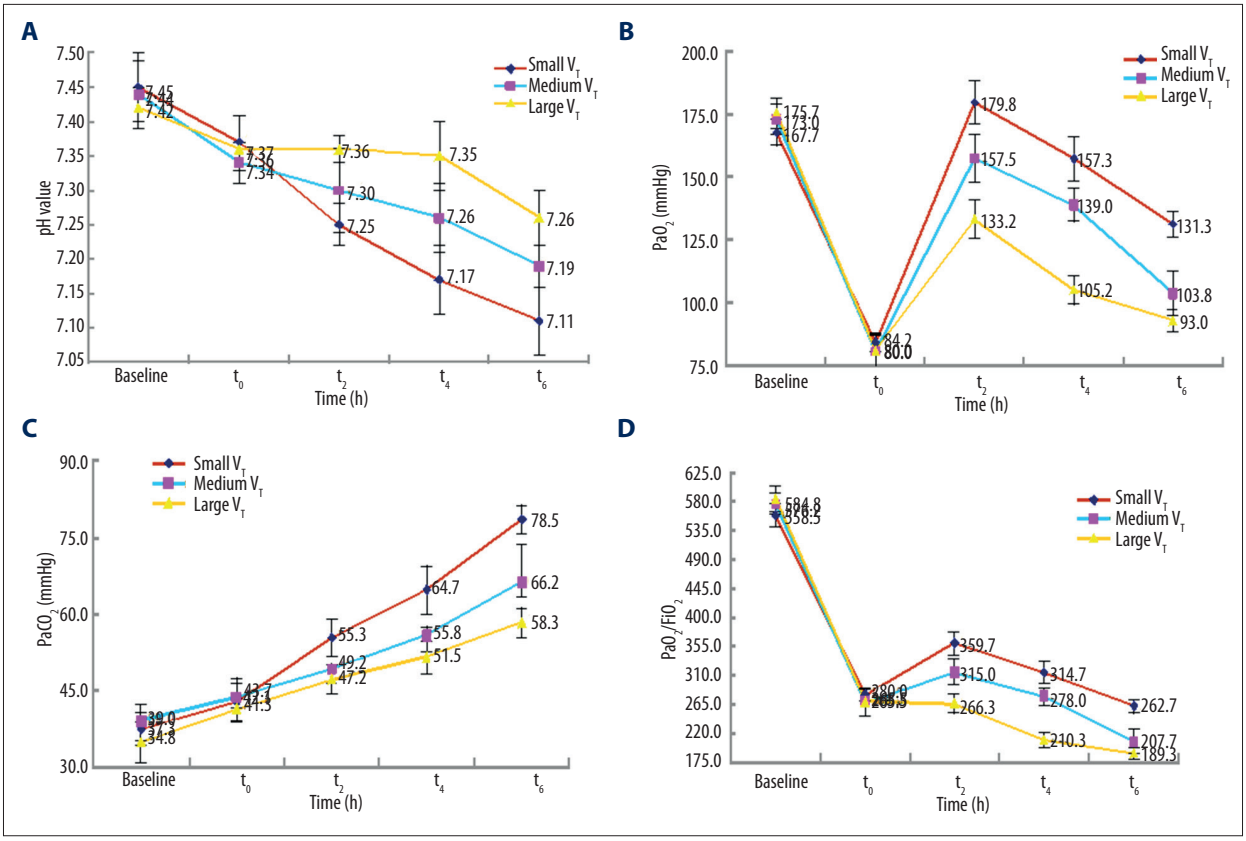

Figure 1. Arterial blood gas analysis and oxygenation index comparison. (**A**) Comparison of PH in the three groups; (**B**) comparison of PaO_2 in the three groups; (**C**) comparison of $PaCO_2$ in the three groups; (**D**) comparison of oxygenation index in the three groups.

Table 2. Comparison of ELWI and PVPI (x±s).

Items	Groups	n	Baseline	t_0	t_2	t_4	t_6
ELWI (ml/kg)	Small V_T	6	11.8±1.5	20.3±1.6*	22.2±2.0	19.5±1.5	17.7±2.4**
	Middle V_T	6	12.7±0.8	18.3±1.2*	24.5±1.8**	22.2±1.9	20.0±1.4
	Large V_T	6	13.2±1.5	19.5±1.9*	25.3±1.8**	27.0±1.4**	29.2±2.1**
F value			1.633	2.380	5.087	32.252	53.499
P value			0.228	0.127	0.021	0.000	0.000
PVPI	Small V_T	6	3.0±0.6	5.6±0.6*	5.3±0.4	5.1±0.3	4.6±0.4
	Middle V_T	6	2.8±0.4	5.9±0.8*	5.6±0.4	5.5±0.6	5.0±0.2
	Large V_T	6	2.5±0.4	5.4±0.4*	5.8±0.5	5.5±0.3	5.4±0.4
F value			1.383	0.784	2.184	1.444	9.358
P value			0.281	0.474	0.147	0.267	0.002

* Compared with baseline in the same group, P<0.05; ** compared with t_0 in the same group, P<0.05.

Discussion

PQ-poisoning patients show acute lung injury, liver and kidney injury, and systemic inflammation. Most patients die of respiratory failure caused by lung injury [7–9] and some survivors showed different degrees of pulmonary fibrosis after treatment [10]. PQ accumulated in the lungs after being absorbed into the blood, which might be related with the amine

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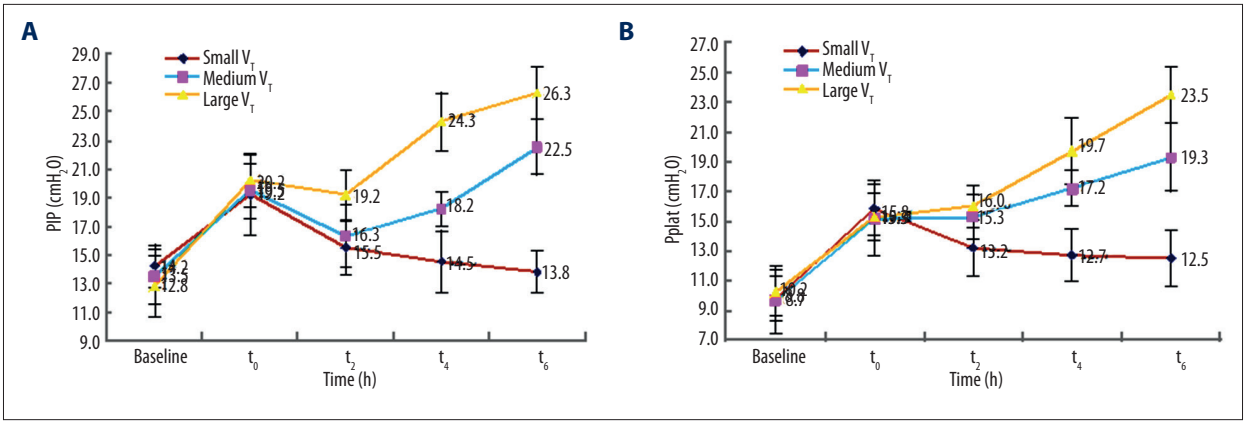

Figure 2. Comparison of airway pressure. (**A**) Trends of PIP in the three groups; (**B**) trends of Pplat in the three groups.

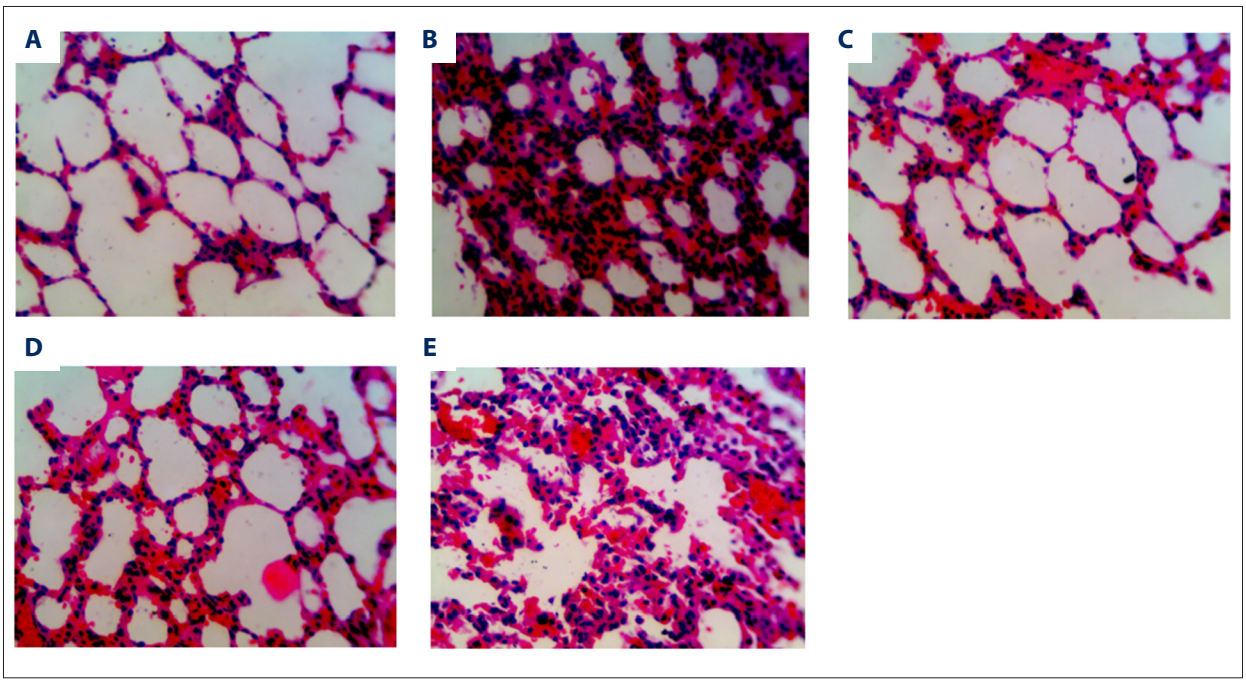

Figure 3. Comparison of lung histopathology (magnification ×400). (**A**) Normal lung tissues; (**B**) model lung tissues; (**C**) small V_T group; (**D**) middle V_T group; (**E**) large V_T group.

uptake system of the lungs [11]. The mechanism of PQ-induced ALI/ARDS is that the cell membrane was damaged by massive reactive oxygen species, which further caused pulmonary hemorrhage, hyaline membrane degeneration, and necrocytosis [12]. The patients showing acute lung injury (e.g., chest stuffiness, dyspnea) develop progressive pulmonary fibrosis and finally die of lung failure [3]. The main pathological changes of PQ-induced ALI were about alveolar capillary membrane damage, which caused pulmonary congestion and edema, reduction of lung volume and ventilation volume, lung compliance decrease, and imbalance of the ventilation-perfusion ratio [13].

The increase of ELWI is one of the most important features of ALI/ARDS and is an important cause of refractory hypoxemia [14]. Application of PICCO to determine ELWI and PVPI has been approved [15]. PVPI is the ratio of pulmonary extravascular fluid/extravascular fluid and is important in determining the mechanism of pulmonary edema. PVPI>3 can distinguish between hydrostatic pressure and pulmonary edema [16–18]. In this study, ELWI increased significantly after modeling success compared with baseline, which reflected the degree of pulmonary edema to a certain extent. PVPI was much higher than the baseline after modeling success, which illustrated that PQ-induced pulmonary edema was a permeability edema.

LPVS has been proposed to treat ALI/ARDS in recent years, which advocated small VT ventilation, permissive hypercapnia, and maintaining alveolus opening by using PEEP [5,19]. Since the currently

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recommended small VT ranged from 6 to 8 ml/kg, we used 6 ml/kg for the small VT in our study. The normal VT of pigs ranges from 10 to 12 ml/kg and we used 10 ml/kg for middle VT. The recommended large VT ranges from 15–20 ml/kg and we used 15 ml/kg [20]. PEEP is mainly set as 10 cmH_2O in animal models, which had little effect on hemodynamics [21]. LPVS combined with PEEP can increase alveolar pressure, promote the reabsorption of alveolar exudate, and reduce inflammation [22]. Application of appropriate PEEP could avoid alveolar collapse, improve hypoxemia, and increase the ventilation efficiency [23]. As reported, the patients in the LPVS group had lower incidence of ventilator-associated lung injury (VALI) and slower progression compared with the conventional mechanical ventilation (CMV) group. $PaCO_2$ and PaO_2/FiO_2 in the LPVS group was much higher than in the CMV group, with a significant difference. In our study, PaO_2 and oxygenation index in the small VT group had a more obvious increase than in the other two groups. Extravascular lung water in the small VT group was less than in the other two groups, which confirmed the treatment effects of small VT ventilation on PQ-induced lung injury. Small VT ventilation can cause CO_2 retention and $PaCO_2$ rise, which can lead to acidosis [24]. We found that $PaCO_2$ rose and PH decreased after ventilation and the PH in the small VT group was the lowest of the three groups. It was considered that the permissive hypercapnia had protective effects on lungs, which might be related with enhanced antioxidant activity and attenuate lipid peroxidation of the lungs [25].

Our study showed that PIP and Pplat increased gradually after mechanical ventilation in the middle and large VT groups. Lung histopathology showed obvious injuries in the middle and large VT groups, which might be associated with airway pressure increase and alveolar overinflation-induced lung injury. Our results further illustrated that large VT ventilation was not suitable for ARDS patients. Menendez et al. reported that overlarge VT ventilation could cause vasoconstriction, reduce endothelium dependent vascular relaxation, and promote hypoxic pulmonary vasoconstriction, which would aggravate lung injury and increase mortality by reducing the expression of α-adrenalin [26].

Conclusions

Small tidal volume ventilation combined with appropriate PEEP can alleviate acute lung injury induced by paraquat, promote gas exchange, and improve oxygenation. LPVS may be a good choice to alleviate the degree of pulmonary edema and improve the oxygenation status after the PQ poisoning patients showed acute lung injury and autonomous breathing was difficult to maintain. Considering that our study was only a short-term experiment, further animal experiments and clinical practice are needed to determine whether LPVS can enhance survival.

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