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Study of the mechanism of pulmonary protection strategy on pulmonary injury with deep hypothermia low flow

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Abstract. – BACKGROUND: The influence of deep hypothermia low-flow (DHLF) perfusion on inflammatory response of pulmonary injury in mammals undergoing the cardiopulmonary bypass (CPB) remains unknown.

OBJECTIVES: This study was conducted to determine the feasibility and mechanism of pulmonary protection strategy on preventing pulmonary function from ischemia reperfusion injury with piglet model.

MATERIALS AND METHODS: Eighteen piglets were divided randomly into three groups: control group with DHLF; continuous perfusion of pulmonary arteries (CPP) with DHLF group (CPP group) and partial liquid ventilation (PLV) with perfluorocarbon (PFC) after CPP with DHLF group (PLV group). Pulmonary ventilation functions in arterial blood samples were measured at pre-CPB, 0h, 1h and 2h until the end of CPB. Inflammatory factor TNF-alpha, IL-8 and IL-6, adherence factor ICAM-1 were also measured.

RESULTS: After CPB, PaO_2 increased but $PaCO_2$ decreased significantly in the PLV group compared with control group. Pulmonary gas exchange in PLV group also improved more significantly than that in CPP group. The expression of TNF-alpha, IL-8 and IL-6 in serum increased more significantly in PVL group after CPB 1h than control group. The extent of lung injury was decreased significantly in PLV than that in CPP group and control group.

CONCLUSIONS: CPP had a protective effect in lung ischemia reperfusion injury during DHLF, and the role of protection lung with maintaining PLV after CPP during DHLF is better than that of single CPP perfusion.

Key Words:
Per fluorocarbon, Partial liquid ventilation, Continuous pulmonary perfusion, Cardiopulmonary bypass, Lung injury.

Introduction

Deep hypothermia with low-flow perfusion (DHLF) is one frequently applied cardiopulmonary bypass (CPB) techniques during cardiovascular surgery for young infants with complex congenital heart diseases[1,2]. Pulmonary dysfunction and constitutional inflammatory response resulting from CPB is a significant cause of postoperative morbidity in these patients[3]. Reports showed that continuous pulmonary perfusion (CPP) was effective in preventing lung injury[4]. Our most recent study indicated that DHLF caused more severe pulmonary injury characterized by increased pulmonary vascular resistance, and impaired gas exchange, and also showed the lung protective effect of CPP with the animal model[5]. Moreover, per fluorocarbon administration during CPP can attenuate inflammatory response[6]. Recently, researchers indicated that partial liquid ventilation (PLV) provides protective effects against inflammatory responses in the lungs of oleic acid-induced immature piglets[7]. PLV is effective in the treatment of infants with severe respiratory distress syndrome, and it can reduce the incidence rate of lung injury[8]. However, the currently available information regarding PLV after cardiac surgery is derived mainly from older children and does not involve DHLF[7,9]. Whether PLV is effective in the treatment of infants with lung injury during DHLF with CPP in immature lung tissue is not known.

Therefore, this study was carried out to determine the effects of PLV and CPP after DHLF on alleviating pulmonary injury of inflammatory response with a piglet model.

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Materials and Methods

Animal Model

Each of eighteen piglets was premedicated intramuscularly with Ketamine 7 mg/kg and atropine (20 μg/kg) before fixing them to the operating table. Continuous thiopental sodium and anatine infusion (20 mg/kg per hour), were injected via ear vein to maintain deep general anesthesia and muscular relaxation. The piglets were mechanically ventilated with the controlled mechanical ventilation (CMV) following the parameters: respiratory rate 12/min, the tidal volume 10-15 ml/kg, and fraction of inspired oxygen 40%-100%. Circuit blood gases were monitored using a blood gas analyzer.

The heart was exposed by median sternotomy. After the animals were given heparin (3 mg/kg), an arterial cannula and a venous cannula were inserted in the ascending aorta and right atrium, respectively, for initiation of CPB. Sodium bicarbonate was given, as necessary, to maintain the base excess between –3 and +3 mmol/L. Alpha-stat blood gas management was used throughout the experiment.

Experimental Groups

Sixteen piglets were randomly assigned to two groups: the DHLF group (n = 6, control group), hypothermic CPB followed by 30 minutes circulatory arrest at 18°C-20°C. The blood of aortic root was blocked, and injected myocardial preservation cold crystalloid cardioplegia (15 ml/kg), and then mechanic ventilation was stopped. After continuous DHLF (50 ml/kg/min) for 60 min, rewarming the blood to 35°C; the CPP group (n = 6), hypothermic CPB followed by 30 minutes circulatory arrest at 18°C-20°C. The blood of aortic root was blocked, and injected myocardial preservation cold crystalloid cardioplegia (15 ml/kg). The perfusion fluid from the catheter with "Y" style in perfusion pump was flowed in the pulmonary artery, and then mechanic ventilation was stopped; the PLV group, after the protocol of the CPP group, the Perfluorocarbon (PFC) was injected into the trachea cannula immediately with the speed of 12 ml/kg/min, and continuous injection of PFC (4 ml/h) was to supplement evaporating liquids.

Measurement of Lung Function

Measurement of lung static compliance, airway resistance, arterial oxygen partial pressure, and carbon dioxide partial pressure to inspiratory oxygen fraction (PaO_2/FIO_2) were detailed in previous study[4]. A piece of lung tissue (about 1 cm^3) from the posterior part of the left lower lobe was cut and its wet weight determined at the different time: before CPB, the moment of CPB (T0), one hour after the end of CPB (T0), and two hour after the end of CPB (T2). The piece of lung tissue was then dried in an oven at 80°C for 48 hours and weighed again to obtain its dry weight for calculation of the wet-to-dry weight ratio.

Analysis of Pulmonary Secretion

Femoral artery blood was collected from different time points: before CPB, the moment of CPB (T0), one hour after the end of CPB (T0), and two hours after the end of CPB (T2). TNF-α, IL-8, and IL-6 were detected by Elisa kit (Sigma Chemical Co., St Louis, MO, USA). The artery blood gas analysis was carried out by CELL-DYN1700 hematology analyzer (Abbott Park, North Chicago, IL, USA).

At the end of CPB, three pieces of lung tissues were cut: one piece was fixed in 4% formalin, and then made paraffin embedded section, and detected intercellular adhesion molecule-1 (ICAM-1) (CD45) expression in lung tissues by immunohistochemistry (IHC) technology; one piece was used to be stained by hematoxylin-eosin (HE), and observed the macrophages of pulmonary edema; one piece was fixed in glutaraldehyde, made section, and observed the change of the pulmonary ultrastructure by using a JEM-200CX transmission electron microscope (JEOL, Tokyo, Japan).

Animal Ethics

All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the 1996 Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health. The Institutional Animal Care and Use Committee at Shanghai Jiao Tong University Research Foundation also approved the protocol.

Statistical Analysis

Statistical analysis was performed using the statistical analysis system (SPSS 11.0, Inc., Chicago, IL, USA). All data are presented as mean ± standard deviation. Two-way repeated measures analysis of variance (ANOVA) was used to test for significant differences. The comparison with one way multiple means was performed by Newman-Keuls method. The *t* test

was used to test the two means. All p values were derived from significance two-sided tests. A p value less than 0.05 was considered statistically significant.

Results

Lung Function

PaO_2 level was measured at different time points of different groups throughout the experimental protocol. The extent of decrease was more significant after the end of CPB in contrast to that before CPB in the intergroup ($p < 0.05$), and it increased significantly at T1 and T2 time points compared with T0 time point ($t = 4.83$, $p < 0.05$; $t = 5.20$, $p > 0.05$, respectively) in the CPP group. In PLV group, PaO_2 level also had difference in T1 and T2 compared with T0 ($t = 6.43$, $p < 0.01$; $t = 10.16$, $p < 0.005$, respectively.

After the end of CPB, PaO_2 level increased significantly at T1 and T2 in the PLV group compared with that in the control group ($t = 9.82$, $p < 0.005$; $t = 13.77$, $p < 0.001$, respectively). PaO_2 level also increased significantly at T1 and T2 in the CPP group compared with that in the control group ($t = 6.45$, $p < 0.01$; $t = 7.16$, $p < 0.01$, respectively). Interestingly, PaO_2 level was statistically significant difference at T2 between the PLV group and the CPP group ($p < 0.05$) (Table I and Figure 1A).

$PaCO_2$ level was significantly higher after the end of CPB than that before CPB in the control group ($t = 3.66$, $p < 0.05$). After the end of CPB, $PaCO_2$ level at T1, T2 was significantly higher in the PLV group than that in the control group ($t = 3.72$, $p < 0.05$; $t = 4.21$, $p < 0.05$, respectively). $PaCO_2$ level at T2 in the CPP group was significantly lower than that in the control group, but it has no significant difference between the PLV group and the CPP group ($p = 0.258$) (Table I and Figure 1B).

The Change of the Inflammatory Mediators in Arterial Blood

TNF-α level increased at T1 and T2 in CPP and PLV group than that in the control group (Table II), but it was significantly higher at T2 in the PLV group rather than that in CPP group ($t = 5.26$, $p < 0.05$) (Figure 2A). IL-8 level had no significant differences between the PLV group and the CPP group ($p > 0.01$) (Table II and Figure 2B). IL-6 level had no significant differences between the PLV group and the CPP group ($p > 0.01$) (Table II and Figure 2C).

The wet-to-dry weight ratio at T2 had significant difference between the PLV group and the CPP group ($p = 0.037$) (Table III and Figure 3).

The Expression of ICAM-1 (CD45) and the Change of Morphology in Pulmonary Tissue

The expression of ICAM-1 was strongly positive in pulmonary tissue of the control groups, but it was moderately positive in the CPP group, and weakly positive in lung tissue of the PLV group (Figure 4). Pulmonary edema was showed in the control group, and alleviated in the CPP group and disappeared in the PLV group observed by HE staining (Figure 5). The transmission electron microscopic showed that the blood capillary alveolar wall degenerated in the control group, showing the severe pulmonary injury. However, slight pulmonary injury was shown in the PLV group (Figure 6).

Discussion

Pulmonary injury after DHLF mainly is pulmonary ischemia-reperfusion injury (LIRI), which is the common postoperative complication of CPB in clinical practice[10]. Cardiopulmonary bypass is associated with a pulmonary inflammatory response, but the mechanism is not known[1,11,12]. This

Table I. PaO_2 and $PaCO_2$ level in PLV group, CPP group and control group ($\bar{x} \pm s$, mmHg).

Index	Group	Before CPB	T_0	T_1	T_2
PaO_2	Control	297.6 ± 39.4	58.5 ± 13.8*	72.6 ± 16.2*	75.8 ± 19.2*
	CPP	301.9 ± 40.6	106.3 ± 22.3*	141.7 ± 26.4*,§	162.5 ± 28.9*,#,§
	PLV	298.2 ± 37.2	102.8 ± 23.7*	179.4 ± 30.1#,*,§	210.6 ± 33.6#,*,§,°
$PaCO_2$	Control	41.2 ± 2.9	64.6 ± 11.2*	66.8 ± 9.8*	68.4 ± 13.6*
	CPP	42.7 ± 3.6	50.6 ± 10.8	49.5 ± 11.1	45.2 ± 21.2§
	PLV	39.1 ± 3.3	51.2 ± 12.9	42.6 ± 9.5§	40.3 ± 9.4§,#

*Compared with before CPB, $p < 0.05$; #Compared with T_0 within groups, $p < 0.05$; §Compared with control group, $p < 0.05$; °Compared with CPP group, $p < 0.05$.

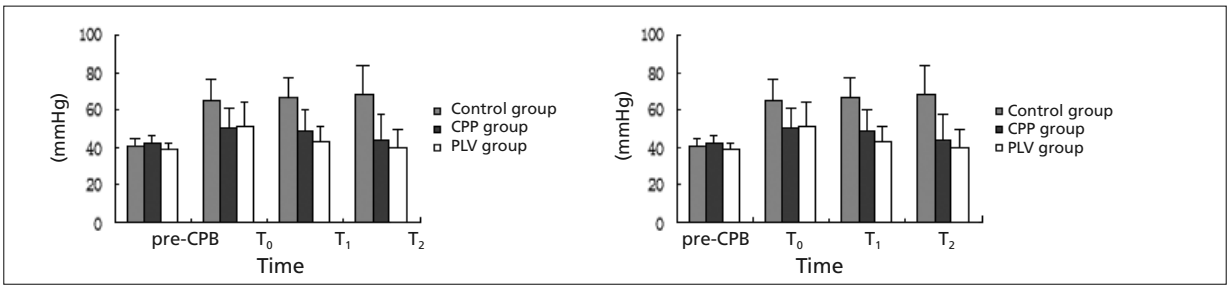

Figure 1. The comparison of arterial partial pressure of oxygen (PaO_2) ***(A)*** and arterial partial pressure of carbon dioxide ($PaCO_2$) ***(B)*** among the control group, the CPP group and the PLV group.

study determined the feasibility and mechanism of pulmonary protection strategy on preventing pulmonary function from ischemia reperfusion injury.

Previous studies showed that the hypothesis that a systemic inflammatory reaction takes place after the use of CPB, could explain most of these effects influences in the lung[13]. The release of various pro-inflammatory cytokines like TNF-α, IL-1, IL-2, IL-6, IL-8, and endotoxin during CPB can lead to the entrapment of neutrophils in the pulmonary capillaries[14,15]. Consequently, the following chain of reactions is likely to occur: an endothelial cell swelling, plasma and protein extravasation into the interstitial tissue, release of proteolytic enzymes, congestion of the alveoli with plasma, erythrocytes and inflammatory debris[16]. In addition, some researchers highlighted the possible pathophysiological mechanisms implicated in the observed postoperative lung dysfunction[3,17]. This study confirmed that the pro-inflammatory cytokines like TNF-α, IL-6, and IL-8 in perfusate after CPB were increased significantly in the control group, which was similar with other report. Meanwhile, the data showed the PaO_2 level was decreased immediately after CPB, and $PaCO_2$ level was increased significantly at the same time in the control group, showing the serious destruction of pulmonary tissue. The pulmonary had the Ischemia Injury, and adhere molecular of pulmonary vascular endothelial cell (ICAM-1, ICAM-2) revealed strong positive expression in the control group, but median positive expression in PLV group, showing the pulmonary protective strategy in PLV group.

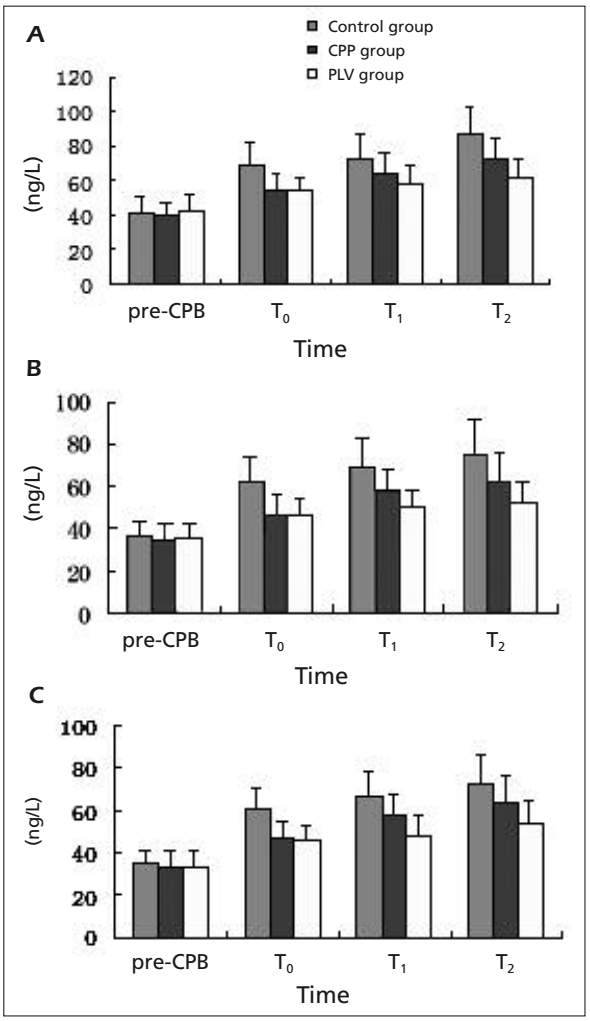

Figure 2. The comparison of cytokines in arterial blood among the control group, the CPP group and the PLV group. A, TNF-α; B, IL-8; C, IL-6.

Pulmonary flow reduced during CPB was a major cause of pulmonary injury after CPB[18]. Reports showed that continuous pulmonary perfusion was effective in preventing lung injury during aortic cross clamping[6,7,19]. This report showed that TNF-α, IL-6, and IL-8 were decreased significantly in CPP group rather than that in the control group with different extent. We showed that the high expression of ICAM-1 in many pulmonary cells, similar with other report. TNF-α can stimulated ICAM-1 expression which combined with leucocyte function-associated antigen 1 (LFA-1) and

Table II. TNF-α, IL-6, and IL-8 content in PLV group, CPP group and control group ($\bar{x}$ ± s, ng/L).

Index	Group	Before CPB	T_0	T_1	T_2
TNF-α	Control	40.4 ± 9.7	68.1 ± 13.7*	72.9 ± 14.3*	86.5 ± 15.9*,#
	CPP	39.3 ± 8.5	53.6 ± 10.5	63.5 ± 12.8*	71.6 ± 12.6*,#,§
	PLV	41.6 ± 10.6	53.1 ± 9.3	58.2 ± 10.7§	60.9 ± 11.2§,*,○
IL-6	Control	34.7 ± 6.5	60.9 ± 10.1*	66.8 ± 11.5*	72.6 ± 14.3*
	CPP	32.9 ± 7.6	46.2 ± 8.4	57.6 ± 10.3*	63.1 ± 12.7*,#
	PLV	33.4 ± 7.2	45.5 ± 7.6	48.2 ± 9.2§	54.5 ± 9.8*,§
IL-8	Control	36.8 ± 6.9	62.7 ±11.2*	69.3 ± 13.5*	75.6 ± 15.6*,#
	CPP	35.5 ± 5.8	46.6 ± 9.6	57.9 ± 10.2*	62.8 ± 12.9*,#,§
	PLV	36.2 ± 6.5	45.7 ± 8.4	49.7 ± 8.9§	52.4 ± 10.6*,§

*Compared with before CPB, $p < 0.05$; #Compared with T_0 within groups, $p < 0.05$; §Compared with control group, $p < 0.05$; °Compared with CPP group, $p < 0.05$.

Table III. The wet to dry lung weight ratio in PLV group, CPP group and control group ($\bar{x}$ ± s, ng/L).

Group	Before CPB	T_0	T_1	T_2
Control	4.06 ± 0.28	6.11 ± 1.02*	6.68 ± 0.67*	7.21 ± 0.69*,#
CPP	4.48 ± 0.32	5.35 ± 1.12	5.85 ± 0.72*	6.26 ± 0.43*,#, §
PLV	4.29 ± 0.41	5.29 ± 0.30	5.31 ± 0.31*,§	5.35 ± 0.46*,§,○

*Compared with before CPB, $p < 0.05$; #Compared with T_0 within groups, $p < 0.05$; §Compared with control group, $p < 0.05$; °Compared with CPP group, $p < 0.05$.

macrophage 1, promoting leukocyte-endothelium adherence[20-22]. We indicated that TNF-α was reduced with the decrease of the expression of ICAM-1 in CPP group rather than that in the control group. During CPP after CPB, enhance oxygenate function and energy exchange between pulmonary alveolar and capillaries, to a certain extent, can maintain cell morphological and functional stabilization immature pulmonary alveolar epithelium cell (Figure 5).

The injection pattern, injection procedure and dosage for the first time were different in different studies[8,23]. In our study, we chose 12 ml/kg as the dosage for the first time with 15-20 min, and then gave the supplement with PFC 4 ml per hour. PFC[24,25] had the strong ability to absorb and release O_2 and CO_2[24,25]. PLV with PFC can increase the PaO_2 in pulmonary alveolar, and enhance the gas exchange between pulmonary alveolar and capillaries[8,26,27]. In our research, we showed the PaO_2 was increased significantly and $PaCO_2$ was decreased significantly at one hour behind the end of CPB. In addition, PFC has anti-inflammatory action to inhibit the TNF-α production, inducing upstream regulation of ICAM-1[20]. Control the expression of IL-8[20], not only can inhibit the aggregation of neutrophil granulocytes, bus also can reduce the expression of ICAM-1 (ligand of CD11b/CD18) and decrease the infiltration of the inflammatory cell from pulmonary alveolar, indicating the anti-inflammatory action of PFC in pulmonary tissue.

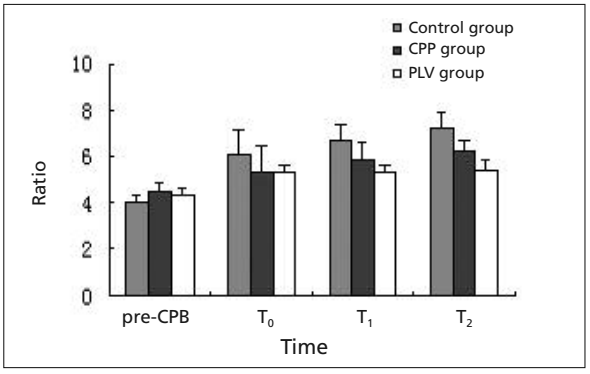

Figure 3. The comparison of the wet to dry lung weight ratio among the control group, the CPP group and the PLV group.

Conclusions

Our study indicated that CPP can reduce he infiltration of the inflammatory cell from pulmonary alveolar to protect pulmonary function. PLV combined with CPP treated DHLF may exert better pulmonary protection action rather than CPP alone.

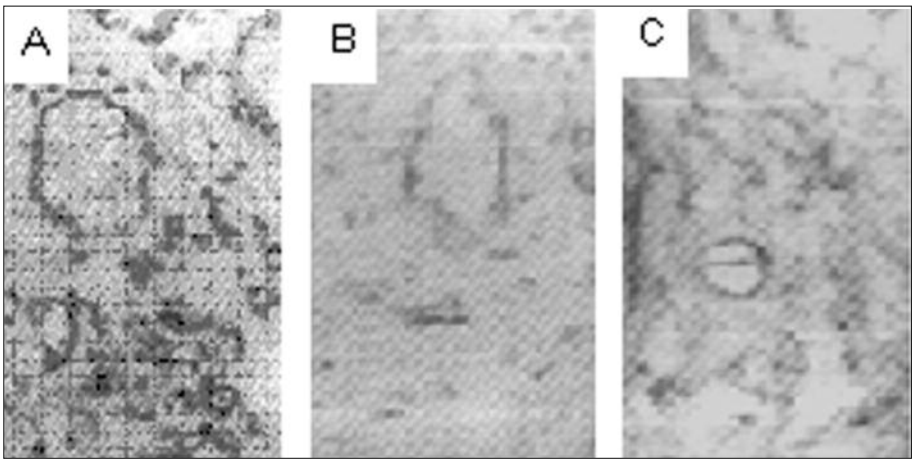

Figure 4. ***A,*** The expression of ICAM-1 in pulmonary tissue in the control group (×400). ***B,*** The CPP group (× 400). ***C,*** The PLV group (× 400).

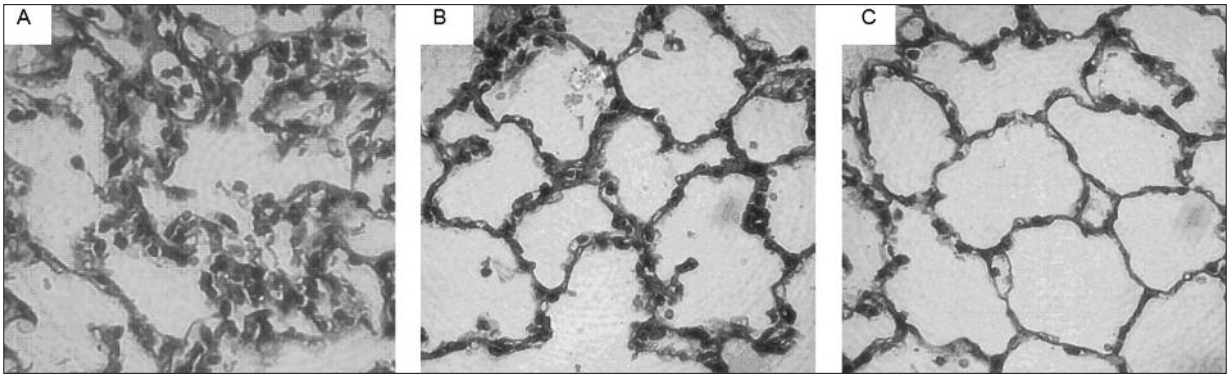

Figure 5. The morphology change of pulmonary tissue by HE staining among the control group ***(A)***, the CPP group ***(B)*** and the PLV group ***(C)***.

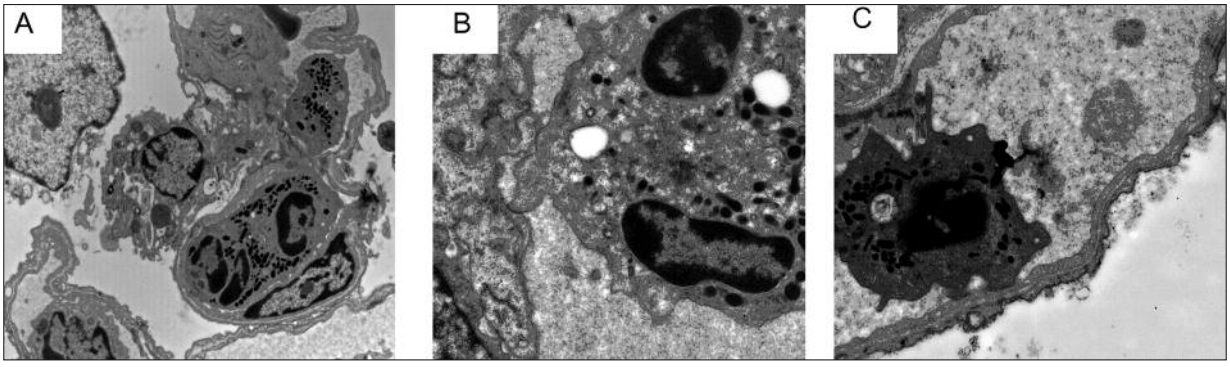

Figure 6. The change of the pulmonary ultra-structure by transmission electron microscope among the control group ***(A)***, the CPP group ***(B)*** and the PLV group ***(C)***.

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